EDINBURGH POST-GRADUATE LECTURES IN MEDICINE

VOLUME FIVE

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FOREWORD

THIS is the fifth volume of the lectures which have been delivered under the ægis of the Honyman Gillespie Trust. It is pretty well known that by the conditions of the Trust these lectures must be delivered in the Edinburgh Medical School and by graduates of Edinburgh. It is also known, although perhaps less widely understood, that the Committee responsible for the lectures works under one limitation—namely that, in deference to the wishes of the testatrix, no lecture may be based on or have reference to animal experiment. The most interesting thing about that limitation is just how singularly little it has cramped the Committee or the individual lecturers.

While it might well be considered fulsome to liken this volume to a precious stone whose lustre becomes appreciable only through the multiplicity of the many facets cut upon it—that is a simile more justly applicable to the School itself—yet these selected essays do show some of the interesting and strangely multifarious lines along which our graduates have been working. The book shows, too, that although we cannot all be research workers we can all observe and we can all—in some measure at least—train ourselves to think for ourselves.

The object of publication is two-fold. One purpose is to provide our readers with food for thought along a variety of professional lines. The other is to rekindle the interest of those who have attended our Post-Graduate Courses. After all, if a medical man is to get the full savour out of his work, one good Post-Graduate Course deserves another, and should whet the appetite for it May this volume prove a further aperitif!

R. W JOHNSTONE
Chairman of Committee

The Committee, which nominates and invites the lecturers, consists of the Professors of the Practice of Physics, Systematic Surgery, and Obstetrics in the University, the Presidents of the Royal College of Physicians and of the Royal College of Surgeons, the Senior non-professorial Physician and Surgeon on the Staff of the Royal Infirmary, the Editor of the *Edinburgh Medical Journal*, and the Chairman of the Post-Graduate Executive Committee Convener

THE ÆTIOLOGY AND DIAGNOSIS OF AMŒBIASIS

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ÆTIOLOGY.—Amœbiasis is primarily an intestinal disease but there may be secondary involvement of the liver and more rarely of the lungs and other organs. It is caused by the tissue parasite *E. histolytica* which gains entrance into the body through the ingestion of contaminated food or water. Although chiefly a disease of the tropics and sub-tropics, where it has proved one of the major problems of the medical services, it is widespread throughout the temperate regions. In fact, individuals infected with *E. histolytica* have been found throughout the world wherever surveys have been made. With the return to this country of many thousands of men from hyperendemic areas the recognition of the condition is of growing importance. The correct diagnosis and treatment of amœbiasis is not only essential for the well-being of those returning with the infection, but is necessary for the prevention of its spread to the general population through the passage of cysts. Cyst-passers may be known to have previously suffered from amœbic dysentery and to have been apparently cured, or they may at no time have shown signs or symptoms of intestinal disease. The term "healthy carrier" is most unfortunate because all available evidence indicates that *E. histolytica* always invades the tissues of its host, although the carrier may be symptom-free at the time the infection is discovered (Bercovitz, 1944). Similarly Adams (1945) considers it advisable to regard every intestinal infection with *E. histolytica* as pathogenic. The disease is spread by the contamination of foodstuffs by the hands and finger-nails of cyst-passers, by means of house flies which can pass cysts unchanged through their intestinal canals, and by the pollution of drinking water supplies The large Chicago outbreak of 1933 which resulted in 1409 proved cases was caused by the pollution of a drinking-water tank by sewage leakage. The incidence of carriers among the staffs of the two hotels whose sewage polluted the common water supply was as high as 37·8 and 47·4 per cent In those countries where human excreta are used for manure, infection is commonly acquired through the consumption of uncooked vegetables In the Far East the spread of the disease is probably mostly by means of flies, and the high standard of sanitation in this country is the chief factor limiting the spread of amœbiasis *E histolytica* can exist in three forms—the active trophozoite, a precystic form, and as a fully developed cyst Only this

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latter can survive any length of time outside the body of the human host. Cysts, however, can live for as long as three weeks and can resist ordinary disinfectants to a remarkable degree, and are unharmed by the routine chlorination of water (Yorke and Adams, 1926). Boiling drinking water and cooking all food is the only safe procedure in endemic areas in the tropics. A patient with acute amœbic dysentery who is only passing active trophozoites is no danger to the community. True epidemics of amœbic dysentery therefore do not occur.

PATHOLOGY.—After their ingestion with contaminated food or drink, cysts of *E. histolytica* pass through the stomach to the small intestine. Trophozoites are then liberated from the cysts and invade the mucosa. The cæcum is the chief site for this invasion, but the lower ileum is said to be attacked also. This invasion is facilitated by the motility of the amœbæ and by the cytolysin which they excrete. They penetrate down to the submucosa and settle down to live on the surrounding tissues, where they are found in a gelatinous substance composed of débris from broken-down cells and mucus. An early lesion consists of a minute nodule which is shown on section to be flask-shaped with its expanded base in the submucosa and a narrow neck leading up to the surface of the mucosa. The body is capable of compensating for the damage done by the amœbæ and so a state of equilibrium may be established. There may thus be only minimal lesions and the infected individual may be symptom-free. Some trophozoites may, however, pass through the precystic stage, form cyst walls and be passed in the fæces whenever the local conditions are not favourable for the amœbæ For local or general reasons not understood the destructive process may at any time advance more rapidly than the body can repair, and when this occurs there will be spread of the disease process with the appearance or recrudescence of symptoms. Necrosis of the superficial mucosa gives rise to small ulcers with a surrounding zone of œdema and hyperæmia with lymphocytic infiltration. If the process continues these ulcers extend down to the muscular coat. Amœbic ulcers are characteristically raised from the surface of the mucosa and have thickened edges which are undermined. The floors of recently formed ulcers are covered with shaggy necrotic material whilst older ulcers tend to have smooth bases At any stage repair may take place by granulation tissue and epithelium grows in from the edges to cover the area This may leave no sign or there may be a typical shallow depression with a shiny base or an obvious scar. If the infection spreads, sinuses are formed which connect one ulcer with another underneath apparently healthy mucosa This disease process may be found in the cæcum, at the flexures of the colon and in the sigmoid and rectum When the process is of long standing the whole bowel wall becomes thickened and fibrosed This change may be patchy and limited to the cæcum or the whole length of the colon may be involved The picture may be altered by the

amount of secondary infection also present. Thus localised masses of granulomatous tissue may be formed in the submucosa and may in time involve all the layers of the bowel wall. Such an amœboma with varying proportions of fibrous and necrotic tissue may be found in the rectum or, less commonly, in the cæcum or other point in the colon It may take the form of a fungating cauliflower mass or simulate an annular carcinoma or tuberculoma The true diagnosis can only be made by histological examination and the co-existence of carcinoma and amœboma has been reported (Morgan, 1944). Ulceration may occasionally proceed to perforation of the gut with resultant general peritonitis or, more often, the formation of a walled-off peri-colic abscess. Another possibility is the erosion of a blood vessel with gross hæmorrhage. This is, however, not common as there is thrombosis of the vessels in ulcerated areas. Chronic cases of very long standing sometimes develop cicatricial stenosis of the colon particularly in its more distal parts.

Microscopic sections of invaded tissues show that amœbæ frequently penetrate the lumina of small veins. Thus trophozoites can readily be carried to the liver in the portal blood stream. The liver cells offer considerable resistance to the amœbæ or liver involvement would be an even commoner complication than it actually is. When trophozoites do manage to establish themselves in the liver they cause liquefaction necrosis of the liver cells in the area with a surrounding zone of hyperæmia. Scattered areas of this kind give rise to the clinical picture of amœbic hepatitis. When either the resistance of the liver is reduced, or the numbers of amœbæ reaching the liver are very high, such areas may extend and coalesce with the formation of an amœbic abscess. The fibrous framework of the liver resists the cytolysin and fibrous tissue is laid down to wall off the cavity. In an uncomplicated case an amœbic abscess contains no pus but only the typical chocolate material composed of shreds of necrotic liver tissue, blood and cytolysed cells. The active trophozoites are found in the walls of the cavity. If, however, there is a bacterial infection, which may be anaerobic, the abscess will contain pus in addition. Amœbic abscess of the liver is most usually solitary, in about 80 per cent of any large series, though two or three may be present. In the tropics, however, multiple abscesses are sometimes found at post-mortem in fumulating cases. A typical liver adscess is most frequently situated at the upper pole of the right lobe of the liver. The diaphram is frequently involved with subsequent rupture of the abscess into the right lung. Owing to the formation of adhesions the pleural cavity is often sealed off and so not infected when rupture takes place The lung may also be the seat of an amœbic abscess by direct blood spread without clinical evidence of liver involvement, but this is a much less common occurrence Such an abscess can be situated at any point in either lung and not necessarily in the right lower lobe The other sites of secondary amœbic infection are very uncommon and need

only be mentioned in passing. A critical review by Watson (1945) has emphasised the rarity of urinary amœbiasis, and the invasion of the skin or gall-bladder, or a brain abscess are also unusual complications. These latter complications, apart from brain abscess, are usually the result of a direct spread of the infection to neighbouring tissues and organs, often following surgical operations.

SYMPTOMATOLOGY.—As can be seen from a consideration of the pathological changes a very varied clinical picture can be produced. The infected subject may be indistinguishable from a normal healthy person or he may suffer from a fatal illness, and between these two extreme conditions all intermediate stages may occur (Hargreaves, 1946). It has been pointed out that any diagnosis from simple indigestion to cancer is compatible with the varied symptomatology of intestinal amœbiasis. Chronicity is its most important feature and Manson-Bahr (1944) has reported that the disease can last thirty to forty years. Less than 1 per cent. show fulminating manifestations of dysentery, and in the majority the picture is atypical (Sawitz, 1943). It is unfortunate that the term "amœbic dysentery" has become in the minds of many medical men a synonym for amœbiasis, since the majority of cases do not show dysenteric symptoms and therefore may be mis-diagnosed through lack of proper investigation.

The onset of symptoms may follow the ingestion of cysts within a few days or be postponed for months or years. Acute dysenteric symptoms are unlikely to be met with often in this country, though abscess of the liver may present itself as an acute illness without a history of previous ill-health. In acute amœbic dysentery the patient usually passes in the twenty-four hours ten or more copious dark motions which contain mucus and blood, and have a foul smell. In contradistinction to bacillary infections there is usually an absence of marked fever, toxæmia or tenesmus. Occasionally a case will show these features and only be correctly diagnosed when it fails to respond to sulphonamide therapy. In the tropics a double infection is not uncommon and a bacillary infection may light up a latent amœbiasis. Cramp-like pain may be localised to the cæcum or sigmoid regions or may be generalised over the abdomen In cases which have had a latent infection palpation may reveal thickening of the cæcum or sigmoid.

In chronic amœbic infection diarrhœa is not a leading symptom and many patients, on the contrary, complain of constipation. A careful history, however, will often elicit the information that there have been occasional short bouts of diarrhœa at irregular intervals When diarrhœa occurs it may only amount to one or two profuse watery stools or a little mucus may be noticed The presence of some obvious blood in the stool may be due to bleeding hæmorrhoids which are a very common accompaniment of this disease. This infrequency of diarrhœa as a principal presenting symptom has been noted recently by Bomford (1944) reporting on service patients with proved amœbic

infections returning to this country. On palpation of the abdomen thickening of the colon may be made out particularly in the region of the cæcum and sigmoid. Tenderness on deep pressure over these areas is very typical, and Manson-Bahr considers that tenderness elicited over the centre of the sigmoid flexure opposite the anterior superior spine of the ilium is pathognomic of amœbic infection. The patients may complain of actual pain in the abdomen or, more frequently, of vague discomfort. Pain when present is often referred to the right iliac fossa and appendicitis may be simulated. Zachary Cope (1946) has sounded a warning against operating too hurriedly for pain in the right iliac fossa occurring in the tropics, as this may be due to amœbic infection of the cæcum and not to inflammation of the appendix. In the Chicago outbreak 32 cases were operated upon as appendicitis with 13 deaths—a fatality rate of 41 per cent. (Strong, 1942). In amœbic typhlitis the colicky pain may come on after meals through the action of the gastro-colic reflex. On palpation tenderness and resistance may be made out over McBurney's point, but it is frequently rather higher up, and in addition there is often tenderness at the lower border of the liver. The diagnosis can be very difficult even when the possibility of amœbiasis is fully appreciated and, in my own experience, I have seen unnecessary laparotomies carried out as well as seen confidently diagnosed cases of appendicitis settle completely under specific anti-amœbic treatment. Amœbic infection of the appendix does occur, but how often this happens is a debatable point and, unless perforation or abscess formation call for surgical intervention, it is only of academic interest as it requires no modification of routine anti-amœbic treatment. More common than actual pain is a complaint of heaviness or vague abdominal discomfort. This is frequently associated with flatulence and periodic distension of the abdomen when on palpation gaseous distension of the cæcum may be observed. There is usually some anorexia and slight dyspepsia. Less definite symptoms are loss of weight, lassitude and depression. Mental depression of mild degree is very common, and the association of so-called tropical neurasthenia with chronic amœbic infection is well recognised. The condition has to be differentiated from neurosis with bowel symptoms. The symptoms of patients with the latter usually clear up with reassurance after a very thorough investigation, including sigmoidoscopy, has revealed no evidence of organic disease.

The clinical picture of amœbic hepatitis is not absolutely clear-cut so that there is a very marked variation in its reported incidence. Many observers report an incidence of from 5 to 10 per cent, whilst Payne (1945) diagnosed mild amœbic hepatitis in 50 per cent. of his series of a thousand cases in Eastern India. The usual picture is that of a generally unfit sallow-looking individual with a muddy complexion but without actual anæmia. Such a case complains of anorexia, dyspeptic symptoms and constant heaviness or an ache in the epi-

gastrium and right hypochondrium. There may be actual pain over the liver which is sometimes referred to the right shoulder. Low-grade pyrexia is often present. On examination the lower edge of the liver is usually palpable and tender and pain may be elicited by pressure exerted over the lower ribs on the right side. Manson-Bahr states that the association of amœbic hepatitis and jaundice is rarely found, but I have seen slight icterus quite commonly and once or twice moderately severe jaundice which cleared up rapidly and completely under treatment with emetine. Greene (1944) has also reported jaundice in 10·5 per cent. of cases of amœbic hepatitis.

Such a clinical picture of subacute or chronic hepatitis by gradually increasing severity of symptoms and signs merges in to the picture of acute liver abscess. The development of symptoms referable to an abscess may sometimes be gradual or the patient may suddenly become seriously ill. Amœbic abscess, though commoner in the endemic areas in the East where it occurs in from 2 to 5 per cent. of amœbic infection, may also occur in this country in men without intestinal symptoms The absence of a definite history of preceding dysentery does not necessarily preclude a diagnosis of amœbic abscess. Ochsner and DeBakey (1939), for example, found in a review of collected cases a history of diarrhœa in two-thirds, and diarrhœa actually present at the time of admission for liver symptoms in only one in five. The symptoms are those already described as being found in amœbic hepatitis but are more severe The temperature tends to be swinging and there is marked sweating and rapid loss of weight. Pain may be very severe and boring in character and either localised to the liver or referred to the shoulder or through to the back or axilla. Occasionally the first indication may be an acute stabbing pain associated with the rupture of an unsuspected abscess into the lung or peritoneum. There is a leucocytosis of 15,000 to 30,000 with polymorphs only increased up to 70 to 80 per cent On examination the liver shows more marked enlargement both upwards and downwards and there may be signs at the base of the right lung with unproductive cough suggesting an early pneumonia or pleurisy. Sometimes there is such guarding of the abdominal muscles that the liver cannot be palpated. Abscess ought to be diagnosed before œdema and bulging of the intercostal spaces occur as the abscess "points" to the axilla or elsewhere

When an amœbic abscess ruptures through the diaphragm into the lung there is usually acute pain in the affected lung, rigors, cough and the expectoration of the typical chocolate-coloured pus when a bronchus is involved In the more unusual event of the rupture being into the pleural cavity the signs and symptoms are those of empyæma. In about 15 per cent of cases of amœbic abscess of the liver the lung or pleura is involved by rupture through the diaphragm.

Primary amœbic abscess of the lung is a much rarer condition, but I have seen two cases in a ward at one time It accounts for about

14 per cent. of all pleuro-pulmonary amœbic infections (Ochsner and DeBakey, 1939). In these cases the symptoms and signs are atypical and pulmonary tuberculosis or an unresolved pneumonia may be diagnosed. There may be general malaise and deterioration of health with either a low grade or swinging temperature with night sweats. Depending on the site of the abscess there may be pleuritic pain and an accompanying friction rub. Cough and expectoration are constant and hæmoptysis common, but the purulent sputum is not characteristic apart from the possible discovery of trophozoites in it. Dormer and Friedlander (1941) failed to demonstrate amœbæ in their series of cases but found eosinophilia of diagnostic importance.

The symptoms of amœboma will obviously vary according to the situation of the tumour mass The most common situation for such a growth is in the rectum or sigmoid and the symptoms may be identical with those of carcinoma in this region. The patient usually gives either a history of definite antecedent dysentery or one suggestive of previous amœbic infection He usually suffers from constipation or alternating constipation and diarrhœa, often with the appearance of streaks of blood and mucus in the stools. He frequently has the feeling of being unable to empty the rectum properly and suffers from tenesmus which is unusual in straightforward amœbic infection. In protracted cases the great loss of weight and strength gives rise to the picture of typical malignant cachexia.

DIAGNOSIS.—The only reliable method of diagnosing amœbic infection is the recovery and identification of the *E. histolytica*. The frequency and rapidity with which a definite diagnosis is made largely depends upon the experience and skill of the microscopist. It is the duty of the clinician, if he does not carry out his own microscopic examinations, to ensure that the most suitable material is sent to the laboratory under the optimum conditions for successful identification. When the search is for trophozoites there is much to be said in favour of bringing the laboratory or at least the microscope to the patient's bedside.

Apart from the actual demonstration of the entamœba in one of its forms, amœbiasis can be diagnosed by a complement fixation test. C. F. Craig (1937), who developed the test, claims that it gives positive results in 90 per cent. of infections, and that it becomes negative when the infection has been successfully eliminated. The test, however, requires to be carried out by an experienced serologist, and other observers have found it only 70 per cent. reliable (Magath and Meleney, 1940). It cannot therefore be employed at present as a short-cut to diagnosis or replace the painstaking search of repeated specimens for the causative protozoa

All individuals suffering from any form of amœbic infection harbour active trophozoites in their tissues, but only in a proportion will vegetative forms be recovered and identified In a large percentage diagnosis will depend upon the discovery of the characteristic cysts.

In his Lumleian lectures Manson-Bahr (1941) reviewed 535 cases and showed that diagnosis was made by the discovery of trophozoites in 41·5 per cent., and of cysts in 53·6 per cent., and that in the remaining 4·9 per cent. the entamœbæ were only found on examination of scrapings taken at sigmoidoscopy. When there is diarrhœa and particularly when the more distal portions of the colon are ulcerated active trophozoites ought to be found, whereas a normally passed stool usually only shows cysts. Trophozoites only retain their motility for a very short time after leaving their host so that stools must be examined "hot." Kershaw (1946) goes even further and suggests that the interval between the shedding of the amœba from the ulcer and its discharge per anum is of importance and that the patient should not delay defæcation. Purgation may ensure a rapid passage of the vegetative forms before they have time to degenerate and become less readily recognisable. The specimen must be taken to the laboratory in the actual bed-pan and not transferred to another container. This allows the pathologist to choose the most likely looking part of the specimen, where there may be blood and mucus on the surface, from which to take his sample. The vegetative form of *E. histolytica* is easily identified when fresh specimens are examined on account of its size, the ingested red cells and its characteristic active progressive motility by means of extruding pseudopodia.

In chronic infections when the patient is passing normal stools only cysts will be found As the cysts may be few in number and scattered in the solid fæces their recognition may be a matter of great difficulty unless a method of concentrating them is employed. Faust *et al.* (1939) by means of the zinc sulphate concentration technique which they introduced found that they doubled the yield of *E. histolytica* cysts discoverable by direct fæcal films. With ordinary iodine stained films of fæces only 40 per cent results were obtained in infected material. This concentration method of Faust's, or some modification of it, ought always to be employed in the search for cysts, as by this technique the washed cysts can be clearly seen and their detail is not obscured by organisms or other contents of the fæces.

Charcot Leyden crystals are often found in the stools, and though not diagnostic of amœbic infection their presence should encourage further search for amœbæ

Sigmoidoscopy can be employed as an adjunct to diagnosis or use to assess progress under treatment or in tests for cure. There is a great divergence of opinion amongst authorities regarding the incidence of lesions visible on sigmoidoscopic examination of individuals with an amœbiasis On the one hand Craig (1943) says that only in 30 per cent. of infected persons are lesions seen in the rectum and sigmoid as amœbiasis is essentially a disease of the cæcum, whilst on the other hand Manson-Bahr (1943) reports lesions in these areas in 80 per cent. of cases. The majority of observers report visible lesions in from 50 to 70 per cent of cases. This discrepancy can probably

be explained by the varying proportions of more acute cases occurring in different series. During an acute phase of the disease sigmoidoscopic examination is unnecessary for diagnostic purposes as active vegetative forms can readily be found in the stools, and such an examination may cause the patient quite marked discomfort or pain. Perforation may occur when very gross ulceration is present, and such a catastrophe has been reported following sigmoidoscopy. In severe cases the rectum will show typical ulcers which can be readily seen by the simple and safe procedure of proctoscopic examination. The chief diagnostic use of the sigmoidoscope is in the investigation of chronic cases in which the examination of the stools has proved negative or indefinite. In these cases the experience of the investigator is of prime importance because, although occasionally quite characteristic ulcers can be seen, in the majority the lesions may be very small and only appreciated by the trained eye. These less obvious lesions are of various types. There may be scattered discrete petechial hæmorrhages without any ulceration or small patches of œdematous mucosa. These may be scattered over an otherwise healthy looking mucosa or superimposed on a generally reddened and velvety surface. Cropper (1945) describes a pin-point crater situated 3 to 6 inches from the anus as the commonest amœbic lesion. This usually takes the form of a small mound about ⅛ inch in diameter projecting from the folds of the mucous membrane and having a minute opening at the apex. The appearance may suggest a little yellow-topped pustule. On scraping these areas with a spoon a little matter may be expressed and on microscopic examination show active trophozoites. In addition to active lesions old ulcer sites may be marked by the presence of small depressed areas. These smaller lesions can often be most satisfactorily seen by smoothing out the surface of the mucosa with the end of the sigmoidoscope when it is being slowly withdrawn.

Another aid to diagnosis which must be mentioned is radiology. This is of particular value in cases of liver abscess where the upward displacement and fixation of the right dome of the diaphragm is often characteristic. X-ray diagnosis in these cases is often the most important and dependable laboratory procedure as preliminary stool examination may be negative, but the need for active treatment be urgent. Yater (1944) believes that thorotrast hepatosplenography is of special value in the diagnosis and accurate localisation of liver abscess, and that it is a safe procedure. Seventy-five c.c. of thorotrast is injected intravenously and films taken two hours later. The drug is taken up by the reticulo-endothelial cells and the normal liver shows a homogeneous density in which the abscess area shows as less dense.

The most important practical point that must be decided is the number of stool examinations that are necessary to confirm a diagnosis of amœbiasis or exclude its presence. No difficulty arises in the cases with dysenteric symptoms, as under these conditions active trophozoites

the vital faculties, its default, that is intermission, their weakness. From this he deduces a simple numerical scheme regarding prognosis: if one intermission is felt after two pulsations, this indicates two grades of strength and one grade of weakness; since one grade cannot overcome two, such a pulse cannot therefore indicate imminent death And even less so a pulse which shows one intermission after a series of ten or twenty beats.

This was not the only instance of intermittent pulse in which Weyer saw recovery The other occurred in his son " Henricus Wierus ", doctor of philosophy and medicine " Because of industrious hard studies in Bonn he fell ill with similar palpitation of the heart, with a disordered *pulsus caprizans* which was often intermittent. But by venesection, undertaken according to good practice, and also by adopting the precepts which, according to our art he judged useful, by God's singular mercy he regained his full health."

For extracts from the original, *see* Appendix I

Weyer's observation was extensively quoted in Gregor Horst's (1578–1637) *Opera medica* (1661), prefaced by an admonition to be cautious in the evaluation of the intermittent pulse, however great the temptation to foretell the future " Though people admire and praise the doctor for nothing so much as his ability to predict the future, since nothing in medical art appears more miraculous than to predict by certain signs approaching recovery and death, nevertheless one should proceed not rashly, but with caution, as Hipp. often counsels; for this reason follows the observation of Wierus regarding the cure of a malignant fever, in which the significance of the intermittent pulse is discussed, and whose words are as follows: " (Follows an extensive quotation of the above observation of Weyer) (*See* Appendix J.)

A similar observation is to be found in Schenck à Grafenberg (1530–1598), particularly interesting since this may be the first report of such an arrhythmia observed by the author on himself On feeling his pulse he found an intermission after a varying number of beats, numbering from four to thirteen, and knowing the very grave significance which Galen attributed to this he was at first filled with the greatest anxiety. But then he noticed to his relief that he could not find anything else wrong with himself, also he was getting on in age and remembered that, according to current views, the intermittent pulse was less ominous at this stage of life So, lest his health become impaired, he took himself in hand, was careful with his diet and avoided food which might obstruct the veins in the heart's vicinity or undermine or weaken the strength of the heart And after nearly a year the pulse became normal again (For extracts from the original, *see* Appendix K)

A similar fortunate outcome was recorded by Amatus Lusitanus (1511–1568). It con- [illegible]

to weakness of the constitution, and, acting on this assumption, he was able to cure his patient by strengthening the heart, withdrawing and then attenuating the humours, and purging With this treatment the pulse changed from being heterorhythmic (which according to Galen denoted a great degree of deviation from normal proportion and harmony) to pararhythmic (a lesser degree of abnormality) and finally to the normal eurhythmic. This may be the first observation in which it was specifically mentioned that the intermission lasted for the time of two normal pulsations (*see* below). This report is also noteworthy in that it contains a primitive tabular presentation of the various kinds of arrhythmic pulse according to Galen's classification. (For extracts from the original, *see* Appendix L.)

The most outstanding seventeenth-century contribution in this connexion is that of [illegible]

in something a diverse manner than in its palpitation or trembling: For in these as to its

motion it is amiss and irregular, in the other as to its rest; for it is sometimes twice as long as it used to be according to its ordinary course.

"First, we ought to distinguish this affection, which (unless I am greatly deceived) hath two distinct ways of being made; For although sometimes the Pulse does intermit, because the Heart ceases for that time from motion; yet besides the Pulse being felt sometimes seems to intermit at the Wrist, whilst the Heart is perceived to shake (as it does in its trembling) most swiftly and incessantly in the Breast· The cause of which I suspect to be, for that this passion of the Heart urging a very little portion only of Blood, is cast forth at every *Systole* into the *Aorta*. Wherefore this being void and growing flaccid, and wanting its load to be moved away; lest it should act so often in vain, it sometimes intermits its contraction, and seems even as in the unloading of a Ship when the wares are more difficultly, and by some let for a time, staid in drawing them forth of the hold, the Porters that carry them are put besides or pretermit some turns of going and coming Further, in malignant or deadly Fevers, if at any time the Pulse be quicker and weak, it also then intermits, the reason for which is not that the Heart sometimes ceases from motion (for it then mostly and incessantly labours) but for as much as the Blood is not carried with enough plentiful provision, by every *Systole* into the *Aorta*, wherefore this wanting work to do, sometimes grows idle

"But moreover the Pulse sometimes intermits, because the contraction of the Heart it self is suspended for a certain time, or its pause is twice longer, which indeed any one may easily find in himself or another, by putting his hand to the Breast, yea those who are sick as often as the Heart ceases from motion, may plainly perceive it in themselves, by the weight and oppression of the Breast. Moreover this affection does not so much happen to the languid, those about to dye, or that are dangerous sick, as to those well enough and as to many things in good order, wherefore it ought not always to be taken according to the opinion of the vulgar for a disease, or for a very pernicious or so hurtful a sign. These who are obnoxious to this, are wont to be troubled for the most part also with the *Vertigo*, the Headach or convulsive Affections But this defect of the Heart as to its type is various, for now the periods of Intermission are certain, and determined to a certain change of the Pulse, to wit, the third, fourth, fifth, or some other more often or more rare, now they are uncertain and wandring, as a cessation now happens after a few Pulses, by and by after more The vibrations of the Artery whilst they are continued are well and strong enough, and for the most part equal, but yet sometimes the first Pulsation is the greatest after the intermission, that which succeeds a little lesser, and so by degrees they are lessened until the intermission comes again, then afterwards a great Pulse beginning, it descends again as it were by a ladder to a cessation

"I have known some (so much as the business could be made known to our observation) that were always endued with an intermitting Pulse, so that I never at any time touching the Artery could find it otherwise, and in the mean time they seemed well enough and complained of no sickness. But however I have known others also to have had an intermitting and more slow Pulse than ordinary, only when a cruel Headach or some more grievous Affection of the Head was present or neer at hand

"From these I think it appears that the cause or formal Reason of the Affection, but now described, does not depend upon the mistion or *Crasis* of the Blood, but only from the irregular dispensation of the animal Spirits from the Cerebel into the Cardiack Nerves, and from thence into the tendons of the Heart: For it may be well suspected that by reason of those Nerves being somewhat obstructed, the animal Spirits cannot descend to the tendons of this Muscle with a full Channel or influx. Wherefore as their provision is something deficient, the Motion of the Heart ceases forthwith for one Pulse, until more plenty of Spirits being restored presently its action is continued So we have seen a Mill driven about by a small Stream, the water sometimes falling and growing scant, to stop or go slow for a

little time, and presently when the water flowed or rose higher, to repeat its rotation or going round.

"Those whose Pulse is great of it self and strong enough, and is wont to intermit, are not only obnoxious to Head-aches and vertiginous Affections, but for the most part also to the *Incubus* and sometimes to the Apoplexy: For if it should happen that the Cardiack Nerves at first not enough open and fitted, should be afterwards wholly obstructed, there will be for that reason a necessity, the Heart (which is the first *Elater*) being made immoveable, that the whole Machine of the animal Body should presently cease from motion and consequently from Life.

"Although this affection having no present disturbances or danger requires not any hasty cure, yet for preservation sake, lest more grievous diseases should follow, Remedies and a certain Therapeutick Method ought to be prescribed, at least the means or way of living, as to the ordering of all things rightly in the whole Life to come; yea a certain light course of Physick, to be observed yearly in the Spring and Autumn is wont to be prescribed, viz that as much as may be all the morbid seminaries lying within the ἐγκέφαλον, or apt to be begotten, may be taken away and provided against."

These writings of Willis are remarkable in several respects. First of all, he pointed out quite clearly, though with certain reservations, that the intermittent pulse is found in otherwise healthy subjects, that it may be present for a long time, and is not a sign of danger. Some of his observations convey the impression of possibly having been made in patients suffering from psychoneurosis in which extrasystoles are known to be a common occurrence. Moreover, he had noticed two essentially different mechanisms underlying this pulse irregularity, namely, on the one hand the omission of one cardiac contraction, and, on the other, the failure of a palpable pulse at the wrist though the heart continued to contract In retrospect this may have been the first distinction between dropped beats and extrasystoles To what extent such interpretation can be given to observations made long before the discovery of auscultation, let alone that of more modern graphic methods, is, of course, doubtful Should this interpretation be correct, some of the features characteristic of premature beats and the good prognosis which is now known to be carried by the majority of extrasystoles would seem to have been attributed by Willis mainly to that variety of the intermittent pulse which would correspond to dropped beats The failure of the palpable pulse to occur at the wrist was attributed by Willis to the small quantity of ejected blood, which is in accordance with modern views and seems to have been entirely overlooked by those who later put forward the theory of hemisystole (*see* below) Another astounding observation was that the intermission is sometimes twice as long " as it uses to be according to its ordinary course "—perhaps the earliest observations that the sum of the intervals preceding and succeeding a ventricular extrasystole equals double the cycle length of the dominant rhythm. Such time relations were to be of fundamental importance for the analysis of extrasystolic arrhythmias more than two hundred years after Willis's paper. Willis also noticed the greater strength of the pulse following an intermission (for an earlier similar observation by Fienus, *see* above) Another striking passage in Willis's paper is his therapeutic advice: the paramount importance of suitable adjustment of the patient's general mode of life in the treatment of this condition has lost nothing with the passage of close on three hundred years.

Lancisi, in 1707, not only expressed himself against the Galenical view of the grave significance of the intermittent pulse, but also supported this by having observed this irregularity in himself for six years, with complete impunity regarding his general health and subsequent disappearance of the arrhythmia:

"And first of all, as far as the abnormalities of the pulse are concerned, although, in some, the inequality and intermittency is such that Galen was able to predict from it Antipater's sudden death, according to our observation this sign is by no means fatal, not only

in children and old people, as Galen asserted, but even in young and strong individuals, when the disease proceeds from poor nutrition of the organs or from the irritation of the hypochondria, where perhaps intermittency of the pulse was constitutional, as in the case of one Oeconomus, whom Galen himself frankly admitted was quite healthy and allowed him to resume his customary occupation Surely if only an intermittent pulse affects a man who otherwise is in good health, this should dissuade the best doctors from foretelling sudden death; rather should this raise in them the hope that it is a slight illness and that he will escape anything more serious and that it can be removed by the appropriate remedy The truth of this I proved by an experiment on myself. For fifteen years, without a break, I had been conscious of the contraction of my heart, and thereafter I had suffered from an intermittent pulse for six years (and I had observed this longer in others), arising from sympathy with the hypochondria. At last, I made a perfect recovery, treating myself with great care, with rhubarb, chalyb and juice of vipers Therefore, in order for the intermittent pulse to be a certain sign of unexpected death it is necessary that all kinds of inequality are joined together, palpitations, shortness of breath, and other similar affections of the chest about which more below " (*See* Appendix M.)

A more specific prognostic significance of certain pulse irregularities formed the subject [illegible]

pending critical diarrhoea, the timing of which could also be foretold by the intermission. If the intermittent pulse was soft, the critical diarrhoea was associated with critical diuresis, if hard, with vomiting. (One wonders whether, in the midst of all this purely speculative and unfounded long discourse there is not here a grain of sense in that Solano might have been aware of the signs of impending uraemia, though the tenor of his disquisition lends little support to the interpretation that anything he wrote was based on observation.) Contrary to Galen, and in conscious opposition to Galen's teaching, he emphasized again and again that such intermittency was a sign of extremely good prognosis The reason of this association between intermittency of the pulse and critical diarrhoea was based on humoral theory and believed by him to be the following In order to rid the body of the morbid material Nature concentrates its strength and efforts on their evacuation and, to achieve this, temporarily suspends other activities, including the pulse beat. Consequently, the larger the quantity of morbid material to expel, the longer the concentrated effort and thus the intermission has to be

The original work is not easily accessible and a few quotations may therefore not be amiss (*see* Appendix N and Fig. 2)

Just as the intermittent pulse indicated impending critical diarrhoea, so " Bispulsación ", that is the *dicrotic* pulse of the ancients, was considered a sign of approaching epistaxis (critical nasal haemorrhage), its time of occurrence could be foretold by the frequency of the " bispulsacion " with one in thirty beats it could be expected in about four days, with one every alternate, or with each beat, within twenty-four hours In a similar way the *pulsus incidiuus* indicated an impending critical sweat The route of elimination seems to have been considered determined by the kind of morbid material to be got rid of

Solano's teaching was considered to be of the greatest importance and attracted much attention beyond the borders of Spain James Nihell went to " the Doctor " especially to study the new doctrine at the source and, according to his *New and Extraordinary Observations concerning the prediction of various crises by the pulse* (second edition, 1750) seems to have been greatly impressed by Solano's teaching. His admiration, however, was not without limits, he thought that there were mistaken inferences from undeniable data, that Solano's rules were too absolute and extensive. But Nihell was lenient in his criticism

"However, such a Mistake was particularly excusable in the Doctor, whose Erudition in *Medicine*, and knowledge of Natural Philosophy, was, according to the unhappy State of Learning in his Country, too weak to counter-balance the deep and overbearing Impressions which *a great Number of new and extraordinary Facts* had made on his Imagination." (Author's italics.)

Others were less critical and more enthusiastic about Solano's great discoveries. For example, Fouquét, while querying some finer details of Solano's views as to the kind of morbid material which produced the several kinds of irregular pulse, defended Solano in no uncertain terms against Nihell's suggestion that lack of erudition might have vitiated his

FIG 2—Solano de Luque, *Lapis Lydos Appollinis* Madrid, 1731 Pp 96 and 97

work· "mais pourtant tout cela vaut son prix, mais les découvertes de Solano dureront au delà des siécles, & les pénibles chef d'oeuvres des *erudits*, semblables à des phosphores légers, n'auront fait qu'éblouir un moment" (*Essai sur le Pouls*, 1767, p. xxvij)

Solano's interpretation was accepted by Laennec (1819, § 675, p. 236)· "La dernière [illegible] découvert par Solano de Lucque." Laennec also accepted Solano's teaching regarding the other varieties of irregular pulse.

Doubts about the universally bad prognostic significance of the intermittent pulse, based on grounds more similar to those of Willis and Lancisi, were expressed by other

writers of the eighteenth century Amongst those may be mentioned E. A. Nicolai (1722–1802). According to his *Theoretische und practische Betrachtung des Pulsschlages* (1746), a distinction should be made between a pulse intermitting " von Natur oder wegen einer üblen Beschaffenheit des Körpers and da ubrigens der Mensch gesund ist " (we would say: constitutionally in an otherwise healthy individual), and that variety due to " widernaturliche Ursachen ", by which he understands conditions of the cardiovascular system, such as polyps, ulcera in the vessels, ventricles or auricles (" Ohrlaplein ").

A similarly more discriminating assessment of the significance of pulse intermissions is found in Senac's (1693–1770) *Traité de la structure du coeur, de son action et de ses maladies* (1749) He enumerates some of the different conditions which may give rise to such intermittency and concludes that because of the varieties of causes the irregularity does not always denote the same condition. In old people the inconstant pulse was due to the hardening of the arteries due to dryness which cause an unsteady flow of the blood and the "spirits" in the nervous tubes. The arrhythmias had a greater importance in malignant fevers He sums up by saying (p 217–8)· "En général, de quelque espece que soient les intermissions, elles ne suffisent pas seules pour qu'on puisse prononcer sur la mort ou sur la vie, si elles sont dangereuses, comme on ne sçauroit en douter, elles se sont souvent terminées heureusement, c'est ce qu'on peut assurer sur le témoignage constant de l'experience, presque tous les Praticiens avouent qu'après des intermissions qui ne paroissoient laisser aucune esperance, divers malades sont parfaitement guéris"

Senac exemplified the intermittent pulse by the failure of a pulse to occur at the third second, assuming an otherwise regular sequence of one pulse per second. From this he distinguished the " pouls intercadent; celui-ci consiste en ce qu'il survient entre deux battements une pulsation qu'on n'attendait pas "—which, in retrospect, may have been the first clear description of an interpolated extrasystole.

Marquet (1747) described the various types of pulse in terms of a special musical notation The normal pulse was expressed as a crotchet between two horizontal lines; normal rate was indicated by such crotchets being put at the beginning of a bar which was divided into five parts by equally spaced vertical lines A minim indicated a large pulse, a quaver, a small pulse and a semi-quaver the vermicular pulse. The position of the note denoted what we could now call the tension· below the lower horizontal line a " pouls concentré ", on the lower line a pulse more difficult to palpate than normal, between the two horizontal lines normal tension, and on or above the upper line types of pulse more easily palpated (" pouls élevé " and " pouls superficiel ") The different clinical conditions which were thought to give rise to the diverse types of pulse were described largely in Galenical terms

Regarding the significance of the intermittent pulse Marquet stated that generally it carried a bad prognosis But amongst the different varieties the " pouls éclipsé ou intercadent " and the " pouls inégal " were considered nearest the normal Regarding the former " il bat régulièrement pendant dix, vingt & quelquefois trente pulsations plus ou [illegible]

only feebly and as a result cardiac systole and arterial diastole were imperceptible, quasi suppressed His observation that this kind of pulse was liable to occur in divers was explained by the fact that they held their breath for a long time and that air compressed in the lungs entered the blood vessels In his musical notation the intermission is indicated by a space without a note, the larger pulse after the intermission by a minim on the upper line in order to signify a larger and less easily suppressed pulse. The stronger pulse after the intermission is attributed to the strong and brusque pulsation of the heart due to the greater quantity of blood in the heart after the intermission. This description seems to be most

suggestive of abortive extrasystoles followed by a large post-extrasystolic beat though dropped beats cannot be excluded. (*See* Fig 3a.)

The " pouls inégal & intermittent ", also considered to approximate the normal pulse was characterized by occasional premature (" un peu précipitées ") pulsations (*see* Fig 3b)

The " pouls inégal & intercurrent ", being without any regularity, seems to correspond most closely to the pulse in auricular fibrillation

19 Exemple d'un pouls éclipsé ou intercadant.

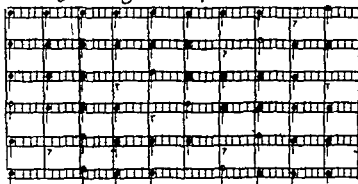


Fig 3a

20 2 pouls inegal et intermittent.

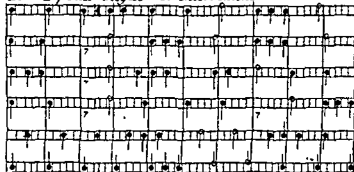


Fig. 3b.

Fig 3—Marquet, *Nouvelle méthode facile et curieuse pour connoitre le pouls par les notes de la musique* 2nd ed, Amsterdam, 1769 Figs 19 and 20.

(For a reproduction of Marquet's musical notation of the *pouls caprizant*, *vide* Bedford.) Marquet, though well known for his method to express the various types of pulse in [illegible] was not the first to do so. More than a century before, Hafenreffer (1587– [illegible] f musical notation, based on the Monochord [illegible] palpating fingers, and some relationship was thought to exist between the " Melodiae Cardinales & Radicales", namely bass, treble, tenor and contralto, and the four elements fire, air, water and earth

Heberden (1710–1801) (paper read on 7th July 1768, published in 1786) denied that the intermitting pulse had any significance: "Some books speak of intermitting pulses as dangerous signs, but, I think, without reason; for such trivial causes will occasion them, that they are not worth regarding in any illness, unless joined with other signs of more moment". He also observed that such arrhythmias may temporarily disappear in patients

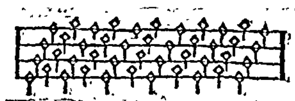


FIG 4a

Intermittens.



Intempestive tempus perturbās modò bis feriendo, *Dicrotus*, modò à saltu seu quodam hiatu capræ Italis Gazellæ dictæ, similitudine sumpta, nuncupatus habetur pulsus *Caprizans*. Sicut enim dictum animal uno & eodem tempore duos saltus efficit, ultimum tamen celeriorem priore, 6. talem & arteria quandoque solet figurare.

Dicrotus. *Caprizans.*

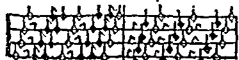


FIG 4b

FIG. 4 —From Hafenreffer, *Monochordon Symbolico-biomanticum*, 1641 *a*. Pulsus moderatus (normal pulse), p 55 *b* Pulsus intermittens, dicrotus and caprizans, p 64

physician ". Amongst such causes he mentions flatus. This may be an early description of what we may now regard as extrasystoles precipitated by way of reflex from the gastro-intestinal tract.

An instructive example of intermittency of the pulse most probably due to anxiety and certainly perpetuated by it, as well as cured by appropriate treatment, is contained in the following passage. It concerns a " certain very experienc'd and judicious professor of physic at Bologna ", who worried greatly about his intermittent pulse; " yet the very same gentleman, after having not disdain'd to take my advice, though a young man, which was to apply his fingers to his pulse much less frequently; and having, in consequence thereof, less increas'd the anxiety of his mind upon the occasion, the intermission soon became much less observable; till at length, by not attending to it, it entirely vanish'd away ". Morgagni had also observed that such intermittency may be due to cardiac factors, or causes in the " neighbouring trunk ", or both, and " then, indeed, I must confess, it becomes a symptom of importance, and we are under a necessity of considering it as such ". In such general form this view is acceptable to-day, for extrasystoles are known to indicate involvement of the heart in infectious diseases as well as sometimes being the first sign of an otherwise asymptomatic coronary sclerosis. Discussing cardiac abnormalities in instances of inter-

we to conclude? Will these causes, which, when separate from each other, are always unable to produce an intermission of the pulse, be always, or almost always, able to produce this symptom when they are join'd together? As, in order to discuss these points properly, a much greater number of observations are requir'd, it will be sufficient at present to have pointed out those things which do not always answer." What an impressive example of

will become apparent as one of the central themes in the course of this book.

Views similar to those of Senac and Heberden were held by Maximilan Stoll (1742–

quoted by Nothnagel nearly a century later (1876).

Skoda (1805–1881) emphasized (1850) that, while disturbances of cardiac rhythm may unquestionably be due to organic cardiac disease, it was certain that the most pronounced

auch seyn mag, kann man deshalb nie den Schluss ziehen, dass eine organische Krankheit des Herzens vorhanden sey ". (p 233.)

However, in spite of such writings, Galen's view held sway until the beginning of the

the " most serious

ery great import ".

acute, but since it

was not indicative of " une altération substantielle de l'organe " it was of no prognostic

contradictory conclusions.)

Fothergill's tabular presentation of arrhythmias contained in his earlier paper of 1870 (*see* Table 1) is a good illustration of the ideas prevailing about cardiac arrhythmias at that time. The complexity of conditions, which may give rise to cardiac irregularities, became increasingly realized and interest shifted to the study of the underlying causes, investigated by experiment and clinical observation.

Cardiac Irregularity is due to Disturbance of Balances in—	1 Vis Inertiae of Blood = Muscular power		
	2 Distension = Irritability of cardiac ganglia + controlling action of vagus	Excessive distension, from temporary action of causes above Imperfect distension—as in severe haemorrhage,—from want of blood to distend the chamber walls Exhaustion of sympathetic,—from fatigue, debauch, withdrawal of nerve-force for purposes of digestion, &c Chronic cerebral disease, &c —(*Richardson*)	
	3 Cardiac Ganglia = Controlling action of the vagus	Action of cardiac neurotics: Paralysing the cardiac ganglia or exciting vagus—	as aconite, Calabar bean, &c

TABLE 1.—From Fothergill, J M (1870) "Cardiac irregularity" *Lancet* **2**, 851.

Of the various factors tabulated by Fothergill, as responsible for cardiac arrhythmias, two seem to have attracted most attention: the rôle played by the cardiac nerves, and disproportion between the strength of the heart and the amount of work it had to perform, with the additional importance of cardiac distension

Traube (1818–1876) was one of the protagonists of the importance of the cardiac nerves. He was the first to specify the *pulsus bigeminus* as a clinical entity (substituting this term for his earlier one of "zweispitzige Wellen" = bifid waves) (1867, 1872), and attributed this arrhythmia to a paralysis of the spinal inhibitory cardiac centres associated with increased irritability of the cardiac component of the inhibitory spinal nerves While Traube has to be given the credit for clearly distinguishing between the dicrotic pulse and *pulsus bigeminus*, by starting a confusion between the latter and *pulsus alternans* he was to obscure the significance of these two conditions for a considerable time to come. Both the bad prognosis, which Traube attributed to the *pulsus bigeminus*, and his explanation of this phenomenon were soon challenged (Rosenstein, 1877), but the confusion between *bigeminus* and *alternans* persisted much longer (for instance, Gerhardt, 1896, Mackenzie, 1902, p 94), (*see* also chapter on "Coupling") Amongst those who considered the action of nerves as important in the origin of cardiac arrhythmias may be mentioned Nothnagel (1876) who emphasized abnormal activity of the automatic cardiac ganglia and the possibility of vagal stimulation by way of reflex, and Baumgarten (1888) who mentioned as causes *inter alia* abnormal conditions in the medullary cardiac centre and disturbances of the cardiac nervous system both in its cerebral and intracardiac portions, also reflexes originating from distant organs. In a way, Tripier's assertion of the constant association of a slow and arrhythmic pulse with epilepsy belongs to this conception

The view that disproportion between the strength of the heart muscle and the amount of work which it has to perform was the main cause of cardiac arrhythmias seems to have played an even greater rôle. This was based on the observation that, in certain circumstances, increase in the resistance to cardiac outflow produced arrhythmias, and led to the belief that such arrhythmias in man signified the presence of heart disease which impaired the heart's contractile power

Knoll and Heidenhain, both in 1872, found experimentally that, in certain circumstances, raising the blood pressure resulted in cardiac irregularities (later confirmed by Hering in 1900, and Rothberger and Winterberg in 1910).

The clinical application of such observations was the assumption that impaired cardiac function, caused by myocardial disease and often associated with distension of its chambers, was the chief cause of such arrhythmias Such views can be found in papers by Fothergill (1870, 1872), Nothnagel (1876, rather guarded inasmuch as he enumerated a long list of conditions including many other than cardiac disease), Riegel (1877), Rosenstein (1877), Dehio (1893, for those instances in which atropine failed to abolish arrhythmias the disturbance was located in the automatic mechanism of the heart itself) In 1893 Mackenzie regarded the bigeminal pulse " as evidence of a jaded heart " and " always associated with evidence of failure of heart power "—a view which he was to change radically in the course of the next twenty years As late as 1898 Riegel, who had extensively studied cardiac arrhythmias, wrote that, from a clinical point of view, the commonest cause of all irregularities of heart action were diseases of the myocardium. The disproportion between cardiac energy and the resistance to be overcome by the heart beat was stressed as an important factor in the production of extrasystoles by Vaquez in 1911; Nefedoff, in a paper published in 1913 from Vaquez's Institute, emphasized that extrasystoles are a sign that the heart is [illegible] "sont d'une [illegible] m which he [illegible]

It may be mentioned parenthetically that, more recently, the part played in the production of ectopic arrhythmias by mechanical distension and stretching has again been considered Fredericq (1924) found in the isolated turtle's heart a decrease in chronaxie with increased mechanical distension of the muscle fibres, Bard (1925) attributed the occurrence of ventricular as well as of auricular extrasystoles to distension and intracardiac changes in pressure; and Scherf, Scharf and Goklen (1949) found a pronounced effect, upon ectopic arrhythmias produced by the topical application of aconitine, on stretching auricular muscle

An interesting interlude is provided by the attempts to explain the intermittent pulse by the assumption of hemisystole, that is, the contraction of only one half of the heart. This idea seems first to have been put forward by Charcelay in 1838. He noticed the absence of a carotid pulse with every other beat while the jugular pulse was present in every beat; with others, only the carotid pulse was noted, without the jugular one He attributed this to " dyschronisme " between the two ventricles and concluded: " En conséquence, qui dit systole du ventricule droit, dit pulsation jugulaire qui dit systole ventriculaire gauche, dit pulsation carotidienne " But the main protagonist of this view was Leyden who, on the strength of observations in one case (1868), attributed the second beat of a *bigeminus* to the isolated contraction of the right ventricle, and on the strength of two additional cases of this kind drew far-reaching conclusions about the underlying mechanism (1875): In cases of advanced mitral incompetence the regurgitating blood was—in his opinion—ejected into the pulmonary capillaries where it met the blood stream of the pulmonary artery and these two streams cancelled one another. The result he believed to be that only with every second beat was the filling of the left heart adequate for producing a pulse. The patent impossibilities of such an explanation were exposed almost immediately by Bozzolo (1876) " mit mehr Witz and Grunden, als Hoflichkeit and Complimenten " (to quote Malbranc's words about this strongly-worded paper of Bozzolo) All the same, the number of leading members of the profession at the time who accepted this view is amazing; they include Gerhardt (1876), Malbranc (1877) who coined the term *Hemisystolia cordis* and accepted it in a modified form, Rosenstein (1876), Friedreich (1878), and as late as 1908 it was not only still accepted by Kraus and Nicolai, but re-iterated by Leyden (and Bassenge)—a remarkable record for an eminent man to adhere for forty years to a patently erroneous view in the face

of numerous publications which refuted it on experimental or clinical grounds: Bozzolo (1876), Riegel and Lachmann (1880), Mackenzie (1893, p 110), Frank and Voit (1900), Hering (1908) amongst them

Other unusual explanations of cardiac irregularities were based on teleological considerations In a way Hodgson's view (1815) belongs to this group He had observed double contractions of the heart with one pulse at the wrist in "contraction of the left auriculo-ventricular opening", this he attributed to two contractions of the auricle to one of the ventricle, these being necessary in order to drive sufficient blood through the stenosed ostium. He considered this of diagnostic significance: "The double pulse at the heart may therefore, I conceive, be regarded as characteristic of contraction of the communication between the auricle and ventricle; and in the absence of this double pulse, violent action of the heart, accompanied by a small pulse in the arteries, may be considered as the diagnosis of obstruction at the orifice of the aorta" This seems an early attempt to use changes of rhythm for diagnostic purposes in valvular disease. Hodgson apparently noticed the greater incidence of arrhythmias in mitral as compared with aortic valvular disease

Fothergill (1870) accounts for the longer diastolic intervals in cardiac arrhythmias thus. "The wearied muscular fibres claim, every now and again, and often very rhythmically, a longer diastole, and fatigue asserts itself in a longer sleep, however the irritant may goad The heart's brief, fitful sleep has its longer and shorter periods of rest, according to its necessities, as has the organism under weariness." Handford (1888) held that "linked beats" (what we would now call extrasystoles) had the function to effect a complete emptying of the ventricles which one contraction was incapable to achieve. Nicolai and Plesch (1909) had similar views regarding extrasystoles occurring in complete A-V block; their function consisted in increasing the ventricular rate and minute volume after exercise because the normal mechanism was absent owing to the block As recently as 1949 a similar observation made in a case of sinus bradycardia with A-V escaped beats was termed "Lebensrettende Extrasystolen" by Katsch and in flowery neo-vitalistic language hailed as a contribution to New Ways of Thought in Medicine

To revert, after this digression, to the historical development of our conceptions on cardiac arrhythmias Until almost the end of last century papers on intermittent pulse were mainly descriptive, and inferences about the clinical significance largely speculative Attempts at some classification, other than purely descriptive, were occasionally made. Some of the work on *pulsus bigeminus* and *alternans* was of this nature (*see* above in this chapter, also chapters on "Coupling" and on "Alternans"). Another instance is the introduction by Sommerbrodt (1877) of the term "allorhythmia" for some periodically recurring alteration in the strength or duration of the individual pulses which, in turn, alternates more or less frequently with normal rhythm or entirely arrhythmic pulses and which usually was a transient phenomenon (p 396) This term, coined for arrhythmias in which a dominant rhythm could be discerned, proved subsequently helpful for distinguishing the complete arrhythmia of auricular fibrillation from other kinds of irregular heart action Baumgarten (1888) distinguished between a deficient pulse during which no heart sounds were audible, and an intermittent pulse, also called *pulsus pseudodeficiens*, in which variety the heart contracted, but the pulse thus produced was too weak to become palpable at the wrist In retrospect this may have been the distinction between dropped beats and extrasystoles (This distinction may have been implied in the paper by Willis, *see* above, and in Laennec's (1819) differentiation between "intermittences" and "fausses intermittences" the latter were "très-facile à distinguer, par le cylindre, d'avec *arrêts* ou *hésitations* du coeur".)

Progress became possible with a better understanding of the physiology of irregular heart action, in particular of the significance of the refractory period, and with the development by Mackenzie in 1892 of a convenient method for recording in man auricular as well as ventricular activity.

The question as to the cause of the heart's rhythmical action has aroused man's curiosity for centuries That it greatly occupied Leonardo da Vinci is evident from his writings of which the following may be quoted (after Keele)·

" And which part of the heart it is which is the cause of the movement; and whether it is inside or outside the heart."

Leonardo seems to have been the first to have thought of a myogenic, and what is more

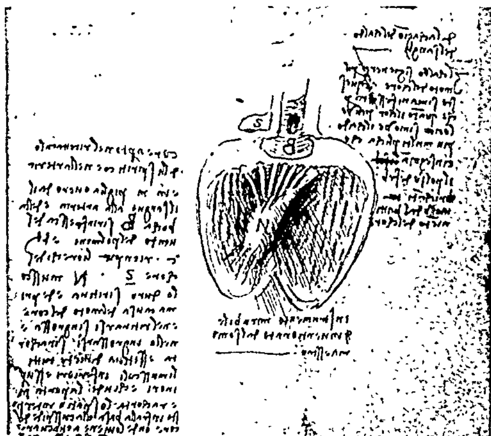


Fig. 5 —Leonardo d- '' An early drawing of the heart ' consider K D Keele (1952).

important in the context of this book, of an automatic origin In an early drawing of the left ventricle he drew a large papillary muscle, labelled it N and wrote

" N, hard muscle, contracts itself, and is the first cause of the movement of the heart." (*See* Fig 5)

" Of the heart This moves on its own, and does not stop, unless for ever."

This is a clear conception of an automatic origin of the heart beat but for the name

Leonardo did, however, also consider the "reversive" nerves (vagi) as an alternative cause of the heart's movement, and although these notes give evidence of an early origin (*ca.* 1500, Keele, personal communication), Keele did not find this subject mentioned again and assumes that Leonardo never found satisfactory answers to these questions

The first to pronounce the heart's action automatic, also in name, seems to have been Borelli In his *De motu animalium*, the first edition of which was published in 1681, two years after his death, he stated· "And these, unless I am mistaken, are sufficient to persuade me that the movement of the heart can be carried out by natural instinct, nay by organic necessity, and moves automatically.

" Nevertheless it will not be superfluous to see whether there are reasons for doubt, or whether the heart is moved not merely by natural mechanical necessity, but by that same animal faculty by which all the other muscles are moved " (*See* Appendix O.)

These words merit to be quoted, not only because of the intrinsic interest of this statement—and the conception of " automatic " will be shown to be of considerable importance in the context of this book—but also because of the historical importance of Borelli " qui, à divers points de vue, doit être considéré comme le point de depart de la route scientifique sur laquelle se recontreront au XIX^{e} siècle J Müller, R. Mayer, H Helmholtz, et depuis, Ch Ludwig et J Marey" (M. del Gaizo, 1909).

Marey is universally credited with the clear formulation of the laws governing rhythmical and arrhythmical action of the heart. In no way does it detract from Marey's great achievement to point out that, more than a hundred years before, Felice Fontana originated the conception of what Marey termed refractory period (Hoff). Fontana suggested that the relaxation of a muscle during prolonged stimulation is due to exhaustion of its store of irritability by the very act of contraction and applied these arguments to the heart: here, the stimulus (believed at that time to be the presence of blood in the chambers) was constant, but though the heart was continually stimulated, chemically as well as mechanically, it relaxed after a time owing to exhaustion of irritability of the heart muscle, the heart rate therefore depended on the rate with which the heart gained and lost its irritability. Fontana should therefore be credited with the discovery of the " refractory period " (Hoff). The first to differentiate between what is now called absolute and relative refractory period seems to have been Schiff (1850) who found that the length of the diastole could be shortened by a modified and stronger stimulus applied at a time when the heart was not yet responsive to the normal stimulus These ideas remained unknown to the majority of physiologists until Marey showed that the phase of absolute non-responsiveness depended on the intensity of the stimulus and on the temperature, and that the forced beat was followed by a longer interval which he termed compensatory pause, as in his opinion it compensated the heart for the increased expenditure of energy incurred by the two preceding contractions the forced beat and the preceding normal contraction (Marey, 1876)

It was not until Engelmann's work (1895) on the mechanism underlying the " compensatory pause " that the understanding of the physiology of these arrhythmias had reached a stage which became applicable to clinical work He showed in experiments on the suspended frog's heart that the interval between the last normal beat preceding an extrasystole [illegible]

the normal pacemaker The next normal impulse reaches the ventricle at a time when it is in the refractory period from the extrasystole and therefore fails to produce a contraction The next ventricular contraction has to await the following normal auricular impulse, therefore the interval between the extrasystole and the following beat is prolonged by an amount which makes the pause compensatory in that the original rhythm is resumed with the first post-extrasystolic beat and thus preserved in spite of the occurrence of the extrasystole The same mechanism obtains in the case of several extrasystoles in succession. Similar conditions were observed with extrasystoles originating in parts other than the ventricles, with the important difference that, in the case of auricular extrasystoles the post-extrasystolic pause usually was shorter than " compensatory ", and with extrasystoles

originating from the *sinus venosus* no lengthening of the post-extrasystolic interval occurred. These laws were soon found to be valid also in the mammalian heart (Cushny and Matthews, 1897)

The application of these physiological discoveries to clinical cases is due to Cushny and to Wenckebach who, in the same year 1899, independently put forward the view that in many instances the intermittent pulse was due to extrasystoles Both these workers arrived at these conclusions by accurate measurements of arterial tracings only and by noticing the similarity in the time relations between the sequence of beats in the radial pulse in man and that of the contractions of the heart as the result of extrasystoles in the experimental animals. The conclusive proof was furnished by Mackenzie's graphic records of the venous pulse which made accurate recording of auricular, in addition to ventricular, activity in man possible and applicable on a large scale. These views were confirmed experimentally by Hering (1900) His statement that a complete absence of lengthening of the post-extrasystolic interval always pointed to the origin of the extrasystole in the large veins was corrected from his own Institute by Pan (1903) who showed that, in certain cases, ventricular extrasystoles may occur in man without producing any change in the sequence of normal beats He thus confirmed the experimental findings of Trendelenburg (1903) and described what are now called interpolated ventricular extrasystoles In the same year Wenckebach summarized the knowledge then available, and for the first time described the arrhythmias, not as disturbances of the pulse, but as an expression of well-defined disturbances of cardiac function The discovery and recognition of the function of the specialized conducting system in the heart and the invention by Einthoven of the string galvanometer were the final steps leading up to present-day conceptions of extrasystolic (and other) arrhythmias The first electrocardiogram of extrasystoles was recorded in 1906 by Einthoven who noticed the abnormal spread of the excitation wave of the premature contraction

SUMMARY

The starting-point in this review of the historical development of our conceptions about certain arrhythmias is the art of feeling the pulse as it was practised in ancient China. It was believed that the site and nature of all diseases could be diagnosed from the pulse alone and various kinds of irregular pulse were described, some of which are briefly discussed In the second century A.D. Galen taught that, with certain differences in degree, the intermittent pulse had, on the whole, a very ominous significance, often indicating impending death Galen's writings are briefly reviewed as far as they are relevant to the assessment of the significance of the irregular pulse. His views held sway until the end of the last, and to a certain extent even into the present century.

In the sixteenth, seventeenth and eighteenth centuries Galen's views were still generally accepted mainly in their original form, though interpreted and modified according to individual observations This is illustrated by the writings of Diversus, Ballonius, Fienus, Lower, Floyer, Friedrich Hoffmann Dissenting opinions are known to have been put forward from the sixteenth century onwards, for example Struthius, Johann Weyer, Schenck à Grafenberg, Amatus Lusitanus, Willis, Lancisi, E. A. Nicolai, Senac, Heberden, Mor- [illegible] indi- [illegible] The [illegible] is the current view in the second half of the nineteenth century; this is exemplified by Fothergill's writings. During that period the rôle played by the cardiac nerves and by disproportion between the strength of the heart and the amount of work it had to perform attracted great attention as being important factors in the causation of arrhythmias. It is pointed out that

until the second half of the nineteenth century papers on the irregular heart action were mainly descriptive, though some attempts at classification were made; these are briefly reviewed. The prognostic significance of bigeminal heart action became obscured by Traube's identification of *pulsus bigeminus* with *pulsus alternans* Some unusual views about cardiac irregularities of that period, including that of hemisystole, are briefly discussed The importance of Marey's work for the understanding of arrhythmias is stressed, although the credit for the first description of what Marey called " refractory period " should be given to Fontana who originated this conception nearly a hundred years before Marey The modern views about the mechanism underlying extrasystolic arrhythmias are based on Engelmann's work on the frog's heart, the essence of which is briefly reviewed Its application to clinical work is due to the independent work of Cushny and of Wenckebach who recognized that in many instances the intermittent pulse is due to extrasystoles The importance of the clinical work of Mackenzie and of the experimental investigations of Hering is briefly mentioned The recognition of the function of the specialized conducting system in the heart and the invention by Einthoven of the string galvanometer are shown to be the final steps leading up to present-day conceptions of extrasystolic and other arrhythmias

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APPENDIX

A Rufus.

[illegible]

B. Galen

[illegible]

ecrhythmi

vel duas vel plures relinquit arteria

Intercidens pulsus est quum inter duos ictus qui ordine proprio concitantur, inde quidam ictus medius intercidit

Deficiens pulsus dicitur in quo non ad duos tantum arteria, sed ad tres etiam et ad plures ictus immobilis perseverat Alii hunc in modum Deficiens est quia magnitudine incipiens ac vehementia magis ac magis subinde minuitur talisque quoad ullam habeat magnitudinem myurus vocitatur; . .

Caprisans pulsus est ubi arteria quum se distendisse apparuerit nec fuerit omnino distenta ad alium perculsum prius quam systoles visionem praebeat praecipitantius transilit; secundo autem fuit percussio facta vehementior

19, 640 Quid differt caprizans a dicroto? Quod caprizans quidem in una systole motus efficit diversos, quemadmodum subsultans capra pedibus salit in aerem; Dicrotus vero bis in eodem pulsat; . .

C. Montagnana

Sed ista ē rō formalis bispulsantis Igit appet in hᵒ iuvēculo cū tremulo motu cordis pulsus bispulsās· qd erat dclarādū. (Sed ista est ratio formalis pulsus bispulsantis. Igitur apparet in hoc juveculo cum tremulo motu cordis pulsus bispulsans quod erat declarandum)

D. Diversus

alterū est, quod in his pulsus quandoque accedit intermittens, qui si supra unicam intermittat pulsationem, magnū periculum minatur, significatque syncope hanc instare, quae intermissio, sicuti & illa praefocatio, non aliunde generatur, quam ex illa sanguinis coalescentis copia, obstruentisque ac gravantis vasa illa & partes internas

E. Ballonius

[illegible]
aut praecipitati senes essent

F. Fienus

[illegible]

G. Hoffmann

Inaequalis vero arteriarum pulsatio, sive mox magna, mox parva, mox celeris, mox debilis, intermittens

H. Struthius

Dum essem apud imperatorem Thurcorum Soltanum Suleimanum Sachum, comperi militem quendam Thurcicum, in acuta febri dicrotum semper obtinuisse pulsum qui post elapsam aegritudinem, nihilo fuit immutatus, cum certis vere convalescentis corporis indicijs unde coniecturam accepi, natura insitu fuisse ipsi huius modi pulsum Plurimum igitur expedit, homines sanos cum medicis saepe conversari, quibus in morbo se sint concredituri Facile enim memoria retinere potest medicus familiaris, qualis in sanitate fuerat

I. Weyer

est consecutus

J. Horst

K. Schenck

L. Amatus

Jacobus Basilius, nobilis Ragusaeus morbo gallico & oculorū suffusione laboraret Caeterum hic cum sit quadraginta quinque annorum, morbis huius successu, ut ego ad eum accedens deprehendi pulsus intermissionem habebat, singularis nanque quatuor vel quinque pulsationibus, arteria deficiebat, remorabatur,

& detinebatur, & te
me, ijs in Centurijs
Centuriae perample
periculosiores haben

M. Lancisi

Et quidem primo quantum spectat ad pulsuum vitia, etiamsi apud aliquos inaequalitas, atque intermittentia tanti fiat, ut inde Gal subitam mortem Antipatro praedixerit, nos tamen signum hoc non solum in pueris, & senibus, ut idem asservit Galenus, sed etiam in juvenibus, & robustis frequenter nullo modo funestum observavimus, cum scilicet ex levi connutritio organorum vitio, vel ex hypochondriorum irritatione procedit, cujus forsitan indolis extitit intermittentia pulsus illius Oeconomi, quem ipse Galenus, tanquam

tione, indeque orta pulsus intermittentia, ex hypochondriorum consensu, per sexennium laboraverim, plus aliis, quam mihi officiosus, & cautus, usu tandem rhabarbari, chalybis, & juris viperati, perfecte convalui Ut igitur intermittentia pulsus improvisae necis certius omen esse possit, necesse est, ut jungatur omni inaequalitatum generi, palpitationi, anhelitui, aliisqui similibus pectoris passionibus, de quibus infra

N. Solano

p 88 After re-stating Galen's view of the very grave significance of the intermittent pulse he goes on to say that he (Solano) believed this " hasta que Dios por su alta, è inexcrutable providencia permitiò, que yo experimentasse ser muy al contrario las mas vezes, como le veras muy presto bastando por aora el que confiesso delante de Dios, que las mas vezes con tal pulso observè que se siguieron maravillosas felizidades "

p 95 La cantidad tambien, siguiendo el mismo sensato rumbo philosofico, no sin confusion de muchos, sospechè por el espacio de las intermissiones, y la experiencia (madre de la verdad) la contesto en la misma forma Adverti, pues, que quando las intermitencias eran largas, ò de mucho espacio, era mucha la copia, ò causa material, que havia que mover, y quando breves, era poca (The evacuation of the morbid material requires a concentrated effort of Nature just as any other activity necessitating a great effort) En este me persuadia el experimento natural, y quotidiano de acà fuera en que vemos, y experimentamos todos, que para cumplir una accion como de alzar mucho material, ò de impeler un grande piedra, ò de luchar con otro, en que sea menester fuerza mucha, è impulso sucesivo, ò largo se recoge por gran rato la naturaleza, privandose en el de otras acciones para arrimar todo el esfuerzo, y virtud, que se divertia en ellas, tan solamente a aquella obra, y en una carrera se nota, que repite el agente los conatos largos, suspendiendo toda otra accion hasta la de respirar, para con las fuerzas unidas dar mas presto satisfacion, à aquel empeño A este modo, quando es mucho el material morboso se suspende, ò recoge mucho para, haciendo mas fuerza, poder impelerlo todo, y por esto se vè la intermission larga, y espaciosa y quando es poca, como no es menester tanto impulso, y conato, con menos tiempo de union de fuerzas, y por consiguiente de menor

to move it, and entirely to exterminate the cause, and thus one experiences that the efforts are less vigorous, and the intermissions shorter) (Our translation)

O. Borelli

Et haec, ni fallor, satis suadent, motum cordis fieri posse naturali instinctu, seu necessitate organica, non secus, ac automa movetur

Nihilominus non erit supervacaneum videre, an adsint rationes dubitandi, utrum cordis motus fieri possit non a mera naturali mechanica necessitate, sed ab eadem facultate, a qua omnes alij musculi moventur

CHAPTER II

DESCRIPTION OF THE VARIOUS TYPES OF EXTRASYSTOLES

VENTRICULAR EXTRASYSTOLES

Ventricular extrasystoles originating in a ventricle, those arising in the stem of the bundle of His should be included, but in view of certain peculiarities of this variety they are discussed in a separate section (*see* p 95)

The Nature of the Disturbance of Rhythm

Fig 6 illustrates diagrammatically the disturbances of rhythm produced by ventricular extrasystoles



FIG 6 —Diagram illustrating the nature of the disturbance of rhythm caused by a ventricular extrasystole The figures indicate intervals in hundredths of a second (except the top row which indicates consecutive numbers of S–A impulses)

It shows three normal beats followed by a ventricular extrasystole. The ectopic stimulus spreads over both ventricles, resulting in a premature contraction, and also is conducted in a retrograde direction over a certain distance, but, in the human heart, usually fails to reach the sino-auricular node as it is blocked below or in the atrio-ventricular node In the majority of cases the next normal stimulus occurs at a time when the conducting system still is in the refractory period of the extrasystole and, not being conducted to the ventricles, fails to yield a contraction. The following normal stimulus (No 5 of Fig 6) reaches the ventricles in the normal way Thus the sinus and auricular rhythms are undisturbed by the ventricular extrasystole, one ventricular contraction occurred prematurely, but as the interval between the extrasystole and the last preceding normal beat plus the post-extrasystolic interval equal the interval between two normal beats the original rhythm is preserved and resumed with the post-extrasystolic beat

We propose to use the following terminology· " dominant rhythm " in order to describe the underlying or prevailing rhythm which is interfered with by the extrasystoles, " coupling " to denote the interval between the beginning of the ventricular complex of the last beat preceding the extrasystole and the beginning of the extrasystole, " post-extrasystolic interval " is called the interval between the extrasystole and the first post-extrasystolic beat When applicable, the term " premature beat " is sometimes used instead of " extrasystole " This terminology seems to us preferable to the one used by Lewis who called the cycles of the dominant rhythm preceding an extrasystole " initial cycles ", the coupling " extrasystolic " or " forced cycle ", according to whether the beat which ends it

is spontaneous or forced by stimulation, the post-extrasystolic cycle "returning cycle" and the subsequent ones "restored cycles".

With a given and constant sinus rate the post-extrasystolic interval (the "compensatory pause") becomes longer as the interval between the extrasystole and the last preceding normal beat (the coupling) becomes shorter (Marey, Cushny and Matthews).

It has been pointed out by Engelmann that if more than one ventricular extrasystole occur, the interval between the first extrasystole and the last preceding normal beat plus the interval between the first extrasystole and the first normal beat, following the series of extrasystoles, equals a multiple of the normal period. If two extrasystoles follow one another at a short interval they usually replace only one normal beat.

These rules are valid only if the normal rhythm is entirely regular, and even if this is the case, the post-extrasystolic intervals often fall a little short of being fully compensatory since the first post-extrasystolic normal beat is conducted slightly faster to the ventricles than the other beats (Engelmann) This observation was confirmed in man by Wenckebach.

The Electrocardiogram

General Features

In the electrocardiogram the typical features of ventricular extrasystoles are premature ventricular complexes of abnormal shape which are not preceded by P waves

The initial deflection, or QRS group, of a ventricular extrasystole is usually either higher or lower as well as wider than those of the sinus beats and commonly slurred and notched. The final deflection, or T wave, while showing many variations, usually is directed opposite to the main deflection of the QRS group, but exceptions occur An RS-T segment often is missing and when present is displaced in the direction of the T wave

These features recall those encountered in bundle branch block and the resemblance is so close that if the record of one individual extrasystole is cut out from a tracing it can hardly be distinguished from the ventricular complex of a case of bundle branch block. Nor is this a coincidence In both conditions the features of the electrocardiogram are due to the fact that one ventricle is activated earlier than the other In the case of ventricular extrasystoles that ventricle is first activated in which the extrasystole originates and, until the impulse has reached the other ventricle, the action potentials of the ventricle activated first are unopposed by those of the other ventricle; higher deflections are thus recorded. The abnormal direction of the spread of the excitation (depolarization) wave and its slower rate of conduction account for the abnormal direction and greater width of the QRS groups respectively, and the abnormal sequence of the subsequent repolarization is responsible for the abnormal T waves It follows that the features in the electrocardiogram of a ventricular extrasystole will become more abnormal the more distal in the conducting system the site of origin of the extrasystole; if an extrasystole originates close to the bifurcation there will be only slight changes; and if the site of impulse is in the stem of the bundle of His, that is above the bifurcation, the extrasystole will give rise to premature ventricular complexes that appear normal. It is also evident that the abnormal width of the QRS group of the ventricular extrasystoles cannot in itself be taken to indicate myocardial disease although exceptionally wide complexes not infrequently are found in patients with structural heart disease (*see* below).

In a large majority of cases of ventricular extrasystoles those of any individual case show in the electrocardiogram a remarkable constancy of form over many years and follow the last preceding normal sinus beat at a constant interval, that is show constant coupling For an early paper on this phenomenon, *see* Lewis and Silberberg (1911). The significance of these observations is discussed in the chapter on "Mechanism".

The record reproduced in Fig. 7 was obtained from a sixty-year-old man without any



Fig. 7 —One ventricular extrasystole occurring after every two sinus beats

signs of structural heart disease. After every second normal sinus beat a premature ventricular complex of obviously abnormal shape which is not preceded by a P wave is visible: a ventricular extrasystole occurred regularly after ever second sinus beat *

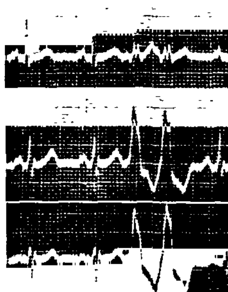


Fig 8 —Two ventricular extrasystoles occurring in succession in each of the standard leads

* The time marker in all tracings indicates 0·04 second, unless otherwise mentioned

The tracings of Fig 8, taken from a forty-one-year-old man, do not show any signs of myocardial damage; in each of the standard leads two extrasystoles are seen to follow one another, replacing one normal beat.

Occasionally the QRS complexes are unusually wide; thus in Fig. 9 they measure 0·18 second. The electrocardiogram indicates infarction of the postero-lateral (basal) portion of the left ventricle Widening of such degree is not rare in patients with structural heart disease and may occur even if the width of the initial ventricular complexes of the sinus beats is within normal limits Such an electrocardiogram indicates a slowing of the spread of the excitation wave, in addition to the other factors already referred to. So far as we are aware, it has not yet been determined from which value the increased duration of the QRS complexes of ventricular extrasystoles can be taken to indicate myocardial damage In cases with bundle bundle branch block, without any other myocardial lesion, the duration of the QRS complexes is 0 12 second or a little less, whereas in those associated with myocardial damage it may greatly exceed this figure



FIG 9.—The standard leads Ventricular extrasystoles with unusually wide initial complexes The sinus beats show the signs of an infarction of the posterior wall Time base 0 05 second

Cases in which the width of the QRS complexes of ventricular extrasystoles is considerably less than that of the sinus beats are rare In Fig. 10a, recorded in an eighty-year-old patient with coronary sclerosis, the sinus beats indicate left bundle branch block After the second beat an interpolated (*see* p 85) ventricular extrasystole occurred, the QRS complex of which measures only 0 08 second as compared with the 0 13 second of the sinus beats Fig 10b, obtained from another patient, illustrates the same phenomenon concerning extrasystoles which were not interpolated Similar cases have been described (Hewlett; Wilson and Herrmann) and interpreted as showing beats originating in the interventricular septum, with symmetrical spread of the excitation wave over both ventricles The presence of a supernormal phase of recovery, resulting in a temporarily improved conduction in the early phases of diastole, has also been considered in this connexion (Simon and Langendorf)

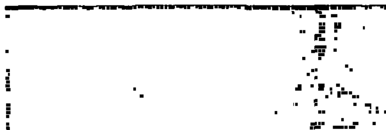


Fig 10—*a*



Fig 10—*b*

Fig 10—*a* Lead I One interpolated ventricular extrasystole the initial complex of which measures only 0 08 second as compared with the 0 13 second of those of the sinus beats *b* Lead V-2 Two ventricular extrasystoles the initial complexes of which measure only 0·08 second as compared with the 0 13 second of the sinus beats

Dressler reported an interesting observation made in a case of bundle branch block with occasional ventricular extrasystoles While the presence of bundle branch block masked the electrocardiographic features of myocardial infarction, this was revealed by alterations in the S-T portions of the extrasystoles A somewhat similar case was described by Simonson *et al* who concluded that the pattern of myocardial infarction or coronary insufficiency may be revealed in ectopic beats in the presence of intraventricular block, and that to a certain extent this is independent of the mechanism producing the ectopic beats (For a similar observation in a case of angina pectoris, *see* Goldhammer and Scherf, Fig 12a)

Alterations, by myocardial infarction, of the QRS complexes of ventricular extrasystoles are illustrated in Figs 11 and 12 Fig 11 was obtained from a sixty-eight-year-old man with clinical signs of acute coronary occlusion The three standard leads do not show any diagnostic features, the deep slurred Q waves and elevated S-T segments in lead V-2, and the low R waves and elevated S-T junctions in V-5 are diagnostic for an anteroseptal infarct The deep Q waves, marked elevation of the S-T junctions and distortion of the S-T segments in the ventricular extrasystoles, as recorded in the chest leads, are noteworthy, and further significant signs of myocardial infarction Fig 12 was recorded in a sixty-nine-year-old man several weeks after an attack of coronary thrombosis. The standard leads and leads

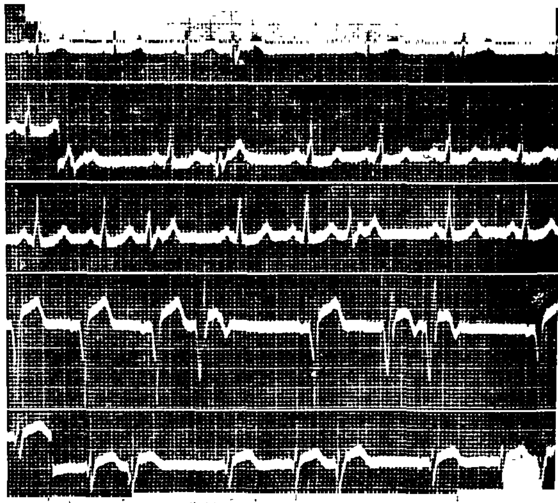


FIG 11 —From above downward the standard leads, V-2, V-5 Changes in the QRS complexes of the extrasystoles For further explanation, see text

V-1 and V-3 are not diagnostic for a myocardial infarction while the deep QS waves in lead V-5 suggest a lateral infarction The features of the ventricular extrasystole recorded in lead V-3 are noteworthy, namely a deep notched QS wave followed by marked elevation of the S-T junction, pronounced distortion of the S-T segment with late inversion of T These *are features commonly seen in lead V-3 in cases of mycardial infarction and it is significant* that, in this instance, they were displayed by the extrasystole while being absent in the sinus beats in this lead For an analogous observation regarding auricular extrasystoles see p. 52 and Fig. 35.

Single and Multiple Extrasystoles

The frequency with which ventricular extrasystoles occur varies greatly in different individuals and in the same individual at different times. If they occur only rarely (intercurrent bigeminy) it may be difficult for the examining physician to record them in an

electrocardiogram and in order to do so it may be necessary to precipitate their appearance by certain measures (*see* p 336). On the other hand, a ventricular extrasystole may follow each beat of the dominant rhythm, producing an arrhythmia known as coupled beats or bigeminal rhythm Fig 13 shows an example, for its further discussion, *see* p 193. One important point may, however, be anticipated, namely, that coupled beats or bigeminal heart action may be produced by a variety of quite different mechanisms and that, for the sake of clarity, such a diagnosis should be qualified and amplified by an indication of the underlying mechanism; for example in the above case. coupled beats (or bigeminal heart action) due to ventricular extrasystoles.

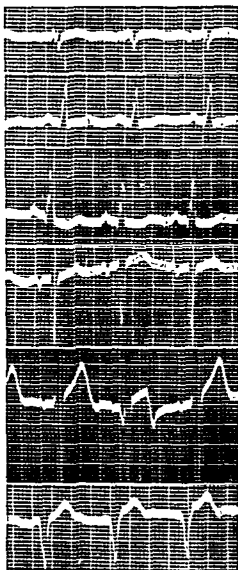


Fig 12.—From above downward the standard leads, V-1, V-3, V-5 For further explanation, see text

If two extrasystoles follow each normal beat, as in Fig 14, the resulting arrhythmia is called trigeminy or trigeminal rhythm In this arrhythmia the two extrasystoles following in succession may have identical shapes in the electrocardiogram, or, as in Fig 14b, they may have different forms. By some the term trigeminy is also used to describe an arrhythmia in which one extrasystole regularly follows two normal beats, as illustrated in Fig 7; this application of the term " trigeminy " gives rise to confusion and should be discouraged.

The use of the terms bigeminal and trigeminal as outlined above is justified on historical grounds. The word bigeminal was originally used at a time when mechanical pulse tracings only were available which, in such cases, showed two successive elevations, often of equal height, before the tracing reverted to the base line. the idea that such two elevations were produced by a " twin contraction " was obvious and led to the name. In the same way a trigeminal pulse was said to exist when a pulse wave was followed by two more elevations before the record returned to the base line this kind of pulse tracing, if caused by an extrasystolic arrhythmia, is now known to result from two extrasystoles following a normal beat, but does not occur if two normal beats are followed by one extrasystole (*see* also Chapter on Coupling, p 193)

If three extrasystoles follow a beat of supra-ventricular origin the resulting arrhythmia is called quadrigeminus, an example is provided by Fig 15 It shows auricular fibrillation, every beat conducted from the auricles being followed by three ventricular extrasystoles The main deflection of the first extrasystoles is directed downwards, the two subsequent



FIG 13.—Continuous ventricular bigeminy owing to one ventricular extrasystole occurring after each supraventricular beat



FIG. 14—a

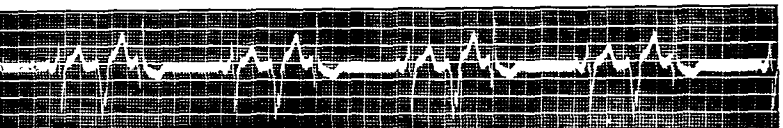


FIG. 14—b

FIG. 14.—Continuous ventricular trigeminy. 14a: lead 3. 14b: lead V-2. From two different patients.



Fig 15 —Lead 3 Auricular fibrillation and continuous *ventricular* quadrigeminy



Fig 16 —*a* Lead I Multiple *ventricular extrasystoles* with gradual slowing of their rate Time base 0 05 second

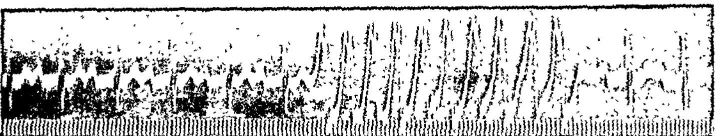


Fig 16 —*b* A short period of paroxysmal ventricular tachycardia



Fig 17 —*Multiple ventricular extrasystoles showing* gradual slowing of their rate The first extrasystole of the dseries coincides with a sinus beat and the resulting complex is a *combination* (or fusion) beat Time base 0 05 secon

ones resemble one another and are mainly directed upwards. The individual groups of four beats are identical in their appearance.

If successive extrasystoles appear in shorter or longer groups, interspersed after several normal beats, the term multiple extrasystoles is employed (Lewis) Fig. 16a, obtained from a case of coronary sinus rhythm, provides an example. If longer groups of ventricular extrasystoles occur, say, ten or more, the term short ventricular paroxysmal tachycardia would be appropriate (Fig. 16b)

If several ventricular extrasystoles follow each other in succession the rate usually remains constant until the chain is suddenly interrupted and sinus rhythm recurs. In some instances, however, the rate gradually slows down, as in Fig 16a. In Fig. 17, which was obtained from a twenty-one-year-old girl, otherwise healthy, a series of five ventricular extrasystoles was recorded The first of these occurred so late in diastole that it coincided with a normal sino-auricular beat so that in the electrocardiogram a transitional complex appeared which was due to a summation of the normal and the extrasystolic complexes. The intervals between the successive extrasystoles gradually lengthened A sinus beat which was due to occur during the long post-extrasystolic pause failed to appear (*see* below in this section, p 43).

The P-Wave of the Blocked Sino-auricular Beat

In the great majority of cases the P waves of the blocked auricular impulses occurring during the post-extrasystolic interval cannot be identified since the small and slow wave is obscured by the far larger and more rapid notched QRS complexes of the extrasystole. Occasionally, however, if the extrasystoles occur comparatively early in diastole, the blocked P wave is visible in the later portions of the QRS complexes or between the QRS complexes and T waves of the extrasystole. This is the case in Fig. 18 which shows two

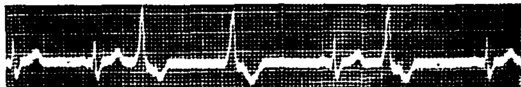


FIG 18 —Lead 2. The blocked P waves of the dominant sinus rhythm are visible in the RS-T segments of the extrasystoles

ventricular extrasystoles occurring in succession, in the final deflections of which normal P waves can be identified; these auricular impulses did not yield ventricular contractions and it therefore follows that the two extrasystoles replaced two normal contractions The ventricular complexes of the conducted sinus beats show abnormal slurring.

Post-extrasystolic Changes in the Electrocardiogram

The following changes in the electrocardiogram may occur immediately after ventricular extrasystoles:

(a) changes in the shape of the ventricular complex of the first post-extrasystolic beat, or rarely of two or more post-extrasystolic beats;

(b) occurrence of heterotopic beats;

(c) occurrence of abnormal pauses

(a) Alteration of the Features of the First Post-extrasystolic Sinus Beat

Changes in the features of the first post-extrasystolic beat are not rare and several types may be distinguished

The commonest variety is that affecting the T waves In some cases such changes go in the direction of normalization, that is inverted T waves in lead 1 may become upright in the post-extrasystolic beat. An example of this is shown in Fig 19 The record, obtained from a forty-six-year-old patient with hypertension (B P. 220/110), shows the pattern of left ventricular strain (left axis deviation, displacement of the RS-T segments and direction of the T waves opposite to the main deflection of the QRS complexes) One ventricular extrasystole is seen in each lead In lead 1 the T waves were deeply inverted, but this wave was

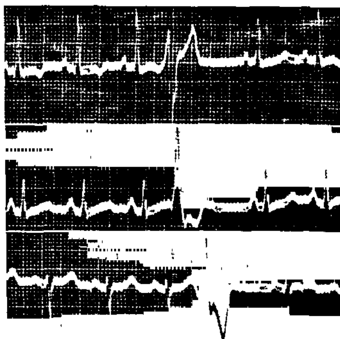


FIG 19 —The three standard leads Marked changes in the form of the T wave of the first post-extrasystolic sinus beat after a ventricular extrasystole

normal in the first post-extrasystolic beat, in lead 3 the T wave of the *post-extrasystolic* beat was lower than the T waves of the other beats; no changes were observed in lead 2.

In other cases changes of the T wave in the reverse direction are observed, namely, upright T waves may temporarily become inverted in the first post-extrasystolic beat. This is shown in Fig. 20, taken from a woman aged seventy-six, a fortnight after a second attack of coronary occlusion The record, lead CR-4, shows that the T wave of the first post-extrasystolic beat was inverted, whereas the T waves of the beats preceding the extrasystoles were upright According to Scherf (1944), inversion of otherwise normal T waves in the first post-extrasystolic beat, even when it occurs in an otherwise normal electrocardiogram, tends to indicate structural heart disease Ashman *et al* (1945) concur with this view, but Videla was unable to confirm this statement

Changes of this kind were occasionally reported in the literature and were seen in man

(White; Bacq; Laubry and Poumailloux; Kapff; Ashman and Hull) as well as in experimental work (Boer; Scherf, 1941). An investigation undertaken to establish the frequency of such changes showed that amongst 168 cases with extrasystoles they occurred in fifty-seven, that is, in one-third of the cases (Scherf, 1944); such alterations of the T waves were seen following ventricular and auricular extrasystoles as well as during auricular fibrillation and A-V block with ventricular arrhythmia. These cases concerned hospital patients, most of them with abnormal hearts. The incidence of this phenomenon among healthy individuals with extrasystoles is certainly lower.

The mechanism underlying this phenomenon is still obscure and may vary in different cases A few relevant considerations may briefly be mentioned.

1. A change of intraventricular conduction may be responsible; conduction may temporarily improve owing to the longer post-extrasystolic interval available for recovery (Fig 22), or be impaired if this interval is inadequate to compensate for the fatigue caused by the two ventricular contractions in quicker succession.

2. The larger diastolic filling during the compensatory pause may produce the changes in the electrocardiogram by altering the size, shape and position of the heart and thereby

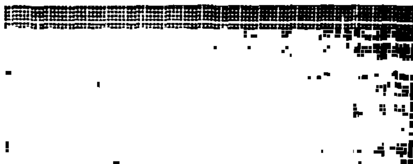


Fig 20—Lead CR-4 The first post-extrasystolic sinus beat shows an inverted T wave, which, in the other sinus beats, is upright

its areas of contact with the surrounding tissues. This may cause changes in the ventricular electrocardiogram by short-circuiting the potentials caused by the depolarization and repolarization of the heart (Lepeschkin) However, if this were the underlying mechanism, alterations of the QRS complexes would also have to occur in every case.

3. A change in the force of contraction of the first post-extrasystolic beat also has to be considered It has been shown that in certain circumstances an extra contraction is followed by stronger contractions (Rihl, Woodworth). This phenomenon, which has been studied in the perfused heart as well as in the heart *in situ*, can hardly be responsible for the changes in the electrocardiogram, as the length of the post-extrasystolic pause was found to be the deciding factor rather than the extra contraction (Scherf, 1944).

4. Changes in nutrition of the heart resulting from the extrasystole were considered responsible by some authors (Katz, Fernbach), but such changes could hardly become manifest so quickly and be confined to one single beat.

5 Changes in contractility and repolarization due to the longer duration of diastole seem so far the most likely possibility (Scherf, 1944)

Recognition of this phenomenon may occasionally be of practical importance, for instance in the differentiation between auricular and ventricular extrasystoles. Fig. 21 provides an example Series of seven and fourteen extrasystoles respectively are seen to follow two supra-ventricular beats The first of these extrasystoles had a different shape,

which was due to its greater prematurity, but later in the series changes again were seen (the sixth extrasystole in each group) without any change in rate Aberrant intraventricular conduction is the most probable explanation for the latter observation (p. 55) Similar tracings were obtained experimentally during auricular flutter following damage of a bundle branch (Scherf, 1929) At first glance the [illegible]

The explanation therefore suggests itself that the higher T wave contained a superimposed P wave and that the extrasystoles were auricular in origin, with aberrant intraventricular conduction Other tracings of the same patient, however, showed that the extrasystoles actually were ventricular in origin and that the difference in the height of the T waves was due to the phenomenon discussed above: the higher T waves of the sinus beats were those found during regular sinus rhythm, but the first post-extrasystolic beats showed considerably lower T waves



FIG 21 —Lead 3 Multiple ventricular extrasystoles The two strips are continuous The first post-extrasystolic sinus beat shows a lower T wave The first and the sixth ventricular extrasystoles of each series are aberrant For further explanation, see text

Changes in the post-extrasystolic beat may not only affect the T waves, but also the QRS complexes, though this is rarer. In one group of cases an intraventricular block temporarily disappears This Fig 22 shows in the top tracing lead 3 from a case with left [illegible] only a delay of conduction was present, the longer interval of recovery available during the post-extrasystolic pause was sufficient temporarily to restore normal conduction.

In other cases lesser changes in the QRS complex of the post-extrasystolic beat are observed, for instance decrease in height or increase in depth of one or the other of its waves

(b) **Occurrence of heterotopic post-extrasystolic beats**

Rarely such post-extrasystolic abnormal beats are auricular in origin. While abnormal P waves of post-extrasystolic beats after *auricular* extrasystoles are common, this is rare in those following *ventricular* ones Slight changes in the P waves following two successive ventricular extrasystoles are shown in leads 2 and 3 of Fig 8 Fig. 23, obtained from a seventy-eight-year-old patient, provides an example of a more pronounced abnormality of this kind The sinus beats show deep Q waves A ventricular extrasystole was followed by a

premature contraction, the P wave of which was inverted. There is no evidence of a retrograde conduction of the extrasystole to the auricle, though this may well have occurred.

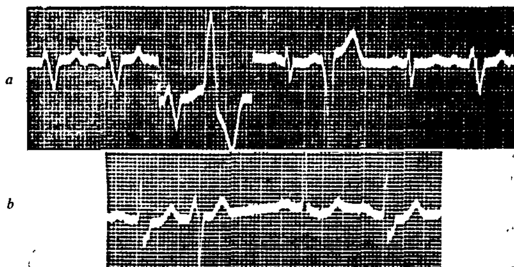


FIG 22.—*a*: lead 3 *b*: lead 2. In both records the signs of intra-ventricular block are absent in the post-extrasystolic beat

More commonly, escaped beats which shorten the post-extrasystolic pause originate in lower centres In Fig 24, which was obtained from a child with respiratory arrhythmia and ventricular extrasystoles, ventricular complexes of normal form and not preceded by P waves were sometimes seen during the post-extrasystolic pauses which they terminated. Such escaped beats arose presumably in the A-V node. A highly-developed automaticity



FIG. 23—Lead 3. Abnormal (inverted) P wave in the premature post-extrasystolic beat after a ventricular extrasystole.

of the lower centres, which is responsible for this condition, is by no means rare and does not indicate the presence of heart disease

Escaped beats originating in a centre below the bifurcation are shown in Fig. 25, taken from a fifty-six-year-old man with moderate hypertension In this case, the ventricular extrasystoles were invariably followed by an escaped beat with an abnormal QRS complex. In the two instances shown the normal post-extrasystolic beat was due a few hundredths of a second later

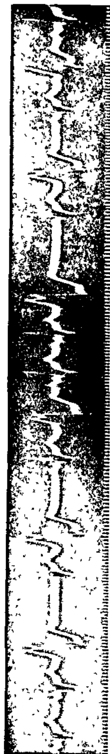


FIG 24 —Escaped beats, presumably originating in the A-V node, following ventricular extrasystoles in a healthy child with respiratory arrhythmia

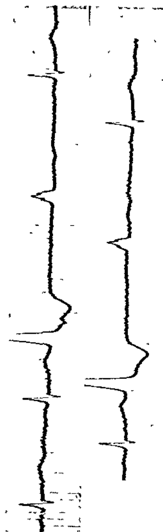


FIG 25 —Lead 2 The two strips are continuous Idioventricular escaped beats following ventricular extrasystoles In the RS-T portion of the first extrasystole an inverted P wave is visible, indicating retrograde conduction of the impulse to the auricles Time base 0 05 second



Fig. 26.—From an experiment on a dog. Records from above downward indicate: signal (stimulation), suspension curve of the right auricle, suspension curve of the right ventricle, electrocardiogram (lead anus-oesophagus corresponding to lead 3), time base 0.02 second. Following five ventricular extrasystoles caused by stimulation of the *right* ventricle, three *left* ventricular extrasystoles of approximately the same rate occurred.



Fig. 27.—Lead 3. Following a series of *left* ventricular ectopic beats a *right* ventricular abnormal beat occurred.

In experimental work abnormal ventricular and/or auricular beats are sometimes found subsequent to stimulation of the heart. Fig. 26 was obtained from a dog whose heart was exposed during an experiment. Stimulation of the *right* ventricle (the last five of a series of nine ventricular ectopic beats are shown, many of which were conducted back to the auricle) was followed by three *left* ventricular extrasystoles. The P waves of first five post-extrasystolic sinus beats show an abnormal form.

Fig. 27 illustrates a clinical observation concerning the occurrence of an abnormal ventricular beat following repeated rapid ventricular excitation. The record, obtained from a sixty-eight-year-old woman, two and a half days after an attack of acute infarction of the posterior wall and twenty-four hours before death, shows auricular fibrillation; the

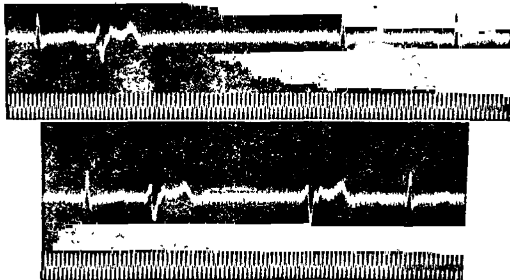


FIG. 28.—The two strips are continuous. Sino-auricular block following ventricular extrasystoles. The second extrasystole is followed by an automatic beat.

last reproduced complex illustrates the shape of the beats of the dominant rhythm. Following an attack of ventricular tachycardia one ventricular complex of an entirely different shape was recorded which indicates that this beat originated in the other ventricle.

(c) Occurrence of Abnormal Pauses after Ventricular Extrasystoles

In rare cases of sino-auricular block the block appears particularly following a ventricular extrasystole. Thus in Fig. 28 an interval measuring twice a normal period, indicating sino-auricular block, followed a ventricular extrasystole. The second post-extrasystolic pause, also due to sino-auricular block, was shortened by an automatic ventricular beat showing abnormal features. The patient had not received digitalis. This phenomenon, which we observed in two cases of sinus block due to digitalis and coronary sclerosis respectively, in one case of coronary sclerosis without digitalis, and in one case with

syphilitic aortitis, may be a vagal effect by way of reflex, each pulse wave producing, via the presso-receptor nerves, a temporary increase in vagal tone sufficient to suppress sino-auricular conduction (p. 64) (*see* also Fig. 17)

In rare cases, during rapid sinus rhythm, the interval between the last sinus beat before, and the first after, a ventricular extrasystole equals *three* cycle lengths of the sinus rhythm *Fig. 29, which illustrates such an observation, was obtained from a seventy-three-year-old* woman with a recent apical myocardial infarction (note the elevation of the R-T junctions and dome-shaped convexity of the R-T segments) The coupling of the extrasystole plus the post-extrasystolic interval equal three cycle lengths of the sinus rhythm. Owing to the sinus tachycardia, two—instead of the usual one—sinus beats were blocked and failed to yield a ventricular contraction.



Fig 29 —Lead CF-5 After one ventricular extrasystole the following two sino-auricular impulses are blocked

During digitalis treatment the escape of centres lower in the ventricles is not rare (*see* p 275) In some of these cases the extrasystoles and the escaped beats have identical shapes in the electro-cardiogram which suggests that both originated in the same centre. Most of such cases also show auricular fibrillation

It is obvious that at a time when only arterial pulse tracings were available for the analysis of arrhythmias, such abnormal post-extrasystolic beats appeared to be definite exceptions to the rules of the compensatory pause and that the nature of such exceptions could not be explained.

SUMMARY

The nature of the disturbance of rhythm caused by ventricular extrasystoles is discussed and the terminology used in connexion with such arrhythmias defined. The electro-cardiographic appearances of ventricular extrasystoles and some relevant features regarding the width of their QRS complexes are discussed. It is pointed out that the frequency with which extrasystoles occur varies widely in different cases Examples are given of trigeminal and quadrigeminal rhythm as well as of multiple extrasystoles and of short ventricular paroxysmal tachycardia Changes in the post-extrasystolic beats after ventricular extra-systoles are discussed under three main headings, namely (1) alteration of the features of the first post-extrasystolic sinus beat, *including the probable mechanism underlying it;* (2) occurrence of heterotopic post-extrasystolic beats; and (3) occurrence of abnormal pauses after ventricular extrasystoles Such changes are discussed in some detail and illustrated by examples.

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AURICULAR EXTRASYSTOLES

Extrasystoles originating in an auricle also produce a disturbance of the ventricular rhythm, but the factors determining the ventricular arrhythmia and particularly the post-extrasystolic pause are more complicated than those prevailing in the case of ventricular extrasystoles

Disturbance of Rhythm

The disturbance of rhythm caused by auricular extrasystoles, three different varieties of which are shown, is diagrammatically illustrated in Fig 30.

The first extrasystole is presumed to have occurred after two normal beats and to have originated rather late in diastole, namely 0 54 sec after the preceding beat, the normal

period measuring 0·80 sec. (Fig. 30a). The extrasystole is shown to be conducted both to the ventricles and over a certain distance in a retrograde direction, towards the sino-auricular node, where the next normal stimulus had begun to be formed and had started to spread over the auricles. Both excitation waves meet and cancel one another since each meets refractory tissue. In such a case stimulus formation in the sino-auricular node is not affected by the extrasystole, the next normal stimulus being discharged at the normal time.

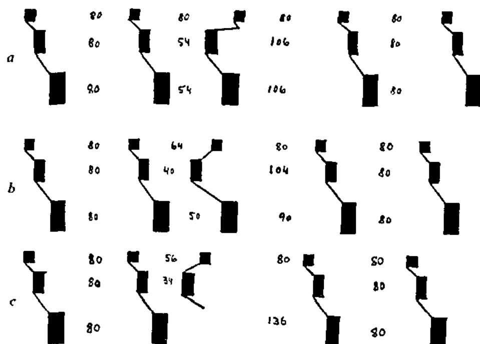


FIG 30—Diagram illustrating the three common disturbances of rhythm

The post-extrasystolic pause therefore is compensatory (Cushny and Matthews; Hering, 1901; Wenckebach, 1903a).

The second auricular extrasystole shown in the diagram (Fig. 30b) is assumed to have occurred earlier in diastole, namely, 0 40 sec after the preceding sinus beat. Again it is shown to be conducted to the ventricles as well as in the reverse direction to the sino-auricular node, but owing to its greater prematurity it reached the latter before the next normal impulse was completely formed There it discharged the immature stimulus and the next normal impulse had therefore to be built up anew. Here again the extrasystole causes a disturbance of the auricular as well as of the ventricular rhythm. Unlike the conditions

prevailing with ventricular extrasystoles, or with the first variety of auricular extrasystoles discussed above, the original rhythm of the heart is not preserved and the post-extrasystolic pause, when added to the coupling of the extrasystole, is shorter than two normal periods, that is, it is not compensatory

Whether or not an auricular extrasystole is conducted in a retrograde direction to the normal pacemaker and reaches it before the discharge of the next normal impulse depends mainly on its time of occurrence in diastole, on the heart rate and on the rate of retrograde and normal conduction If the extrasystole occurs early in diastole and the heart rate is slow, the extrasystole is likely to reach the normal pacemaker, particularly if the rate of retrograde conduction is high Thus in certain fishes with slow heart rate (40–50 per minute), in which the retrograde conduction is faster than that in the normal direction, backward conduction of the extrasystole to the sinus is the rule when the extrasystole occurs within the first fourth to third of the auricular cycle In the tortoise, in which the heart rate is also slow (20–30 per minute), such backward conduction is usual In the amphibian heart, on the other hand, in which retrograde conduction is slow and, by comparison with the tortoise, the heart rate is higher (about 40), and in reptiles with a higher normal heart rate (lizards, snakes), auricular extrasystoles as a rule do not affect the impulse formation in the sinus and the post-extrasystolic intervals are therefore compensatory (Skramlik)

In the mammalian heart and in man, in the majority of cases, auricular extrasystoles disturb impulse formation in the sino-auricular node, and post-extrasystolic intervals that are shorter than compensatory ones are far commoner, their existence became known soon after the importance of extrasystoles in the causation of arrhythmias was realized (*see* p. 19) Gallavardin measured carefully the post-extrasystolic intervals in thirty-seven instances of auricular extrasystoles They were found to be compensatory in eleven instances (thirty-one per cent) The later in diastole an auricular extrasystole appeared the more frequently was the post-extrasystolic pause compensatory.

Whereas the length of the *compensatory* post-extrasystolic pause, whether following a

ing auricular extrasystoles which disturb the stimulus formation in the sinus node One important factor is the time required for the auricular extrasystole to be conducted from its focus of origin to the sinus node. This time will increase with the distance between the focus of origin of the extrasystole and the sinus node Thus extrasystoles arising near the head of the sinus node will reach this node in a very much shorter time than those originating at a distance, say, near the A-V node. Exact measurements showed this assumption to be valid (Lewis, Meakins and White) The rate of the reverse conduction of the extrasystole to the sinus node will also be important; the more premature the extrasystole the slower the rate of conduction (Wenckebach, Drury and Brow, Drury and Regnier).

formation in the centre, and his experiments showed that such inhibition is greater the more damaged the heart muscle Inhibition of stimulus formation by an extra-stimulus has been studied extensively in the automatically-beating ventricle (Erlanger and Hirschfelder, Hofmann and Holzinger, Rothberger and Winterberg, Rihl, 1913a; Miki and Rothberger, Scherf and Shookhoff, 1925, 1926, Eccles and Hoff), but Lewis, White and Meakins pointed out that in this respect the sino-auricular and atrio-ventricular nodes differ from centres producing idioventricular rhythm the S-A and A-V nodes show inhibition of stimulus formation as a result of an extraneous stimulus only if they are poorly nourished or the heart is in a hypodynamic condition (conditions which can occasionally be assumed to prevail in the human

heart with this kind of arrhythmia). It was also shown that such inhibition of stimulus formation is greater when the extrasystole is early, or when there had been several extrasystoles in succession (Hofmann and Holzinger). These results were confirmed by Lewis, White and Meakins. Miki and Rothberger, who devoted a special study to the re-examination of the problem, emphasized the importance of the inhibition of stimulus formation, and also found that the post-extrasystolic intervals were lengthened particularly towards the end of an experiment or when the heart had been damaged by asphyxia, quinine or muscarine

Whereas all the factors discussed so far tend, on the whole, to render the post-extrasystolic interval longer than the interval between two normal beats, this disturbance of rhythm is rendered less conspicuous in the ventricular rhythm as a result of differences in the rate of conduction to the ventricles of the extrasystole and the post-extrasystolic beat Not infrequently auricular extrasystoles are conducted to the ventricles more slowly than the sinus beats and this tends to be the more marked the earlier in diastole the extrasystole occurs. The first post-extrasystolic sinus beat, on the other hand, is conducted at the normal rate, or faster, with the result that the arrhythmia is less marked in the ventricular than in the auricular rhythm. Moreover, the post-extrasystolic interval will be shortened if it is terminated by an escaped beat of idioventricular origin.

To sum up, the length of the post-extrasystolic ventricular interval after auricular extrasystoles will depend on

1. the rate of the prevailing sinus rhythm,
2. time of occurrence in diastole of the extrasystole,
3. sinus arrhythmia, itself dependent on nerve tone,
4. distance of point of origin of the extrasystole from the S-A node;
5. rate of retrograde conduction of the extrasystole to the S-A node;
6. degree of inhibition of stimulus formation in the S-A node by the extrasystole, dependent on the condition of the heart and perhaps vagal tone;
7. rate of conduction of the extrasystole and of the post-extrasystolic beat to the ventricles,
8. presence or otherwise of an escaped beat terminating the post-extrasystolic interval.

In view of the number and complexity of these factors it is easily understood that in an individual case it is hardly possible to explain the time relations with any degree of certainty, especially as a temporary slowing of the heart also has to be considered as an accidental factor (Lewis, 1925). In man the first few cycles following auricular extrasystoles are occasionally shortened (Gallavardin)

If for any reason the conducting system is incapable of conducting the extrasystole to the ventricles, the extrasystole is said to be blocked and will fail to yield a ventricular response. This condition is illustrated in the third extrasystole of the diagram of Fig. 30 (Fig 30c)

The Electrocardiogram of Auricular Extrasystoles

In the electrocardiogram auricular extrasystoles are characterized by premature P waves of normal or, more often, of abnormal shape; in the case of conducted extrasystoles such P waves are followed, after a normal or lengthened interval of conduction, by a ventricular complex of normal (supra-ventricular) or abnormal shape; in the case of blocked auricular extrasystoles such P waves are isolated and are not followed by a ventricular complex.

With auricular extrasystoles the coupling is measured from the beginning of the P wave of the last normal beat preceding the extrasystole to the beginning of the P wave of the extrasystole.

The Shape of the P Waves

The shape of the P waves of an auricular extrasystole depends primarily on its focus of origin, but in certain circumstances is also influenced by abnormal spread of the excitation wave within the auricles, that is, by intra-auricular disturbances of conduction. The first of these two factors is by far the more important

Auricular extrasystoles originating in the neighbourhood of the head of the sinus node give rise to P waves of the same form as the P waves of the prevailing sinus beats (*see also* section on sinus extrasystoles) Extrasystoles springing *from foci situated elsewhere in the auricles yield P waves of different shapes*, they may be taller, smaller, wider, slurred, notched, inverted or isoelectric in one or the other lead Attempts have been made to deduce the focus of origin of the extrasystoles from the shape of the P waves in various leads, they are discussed on p 401

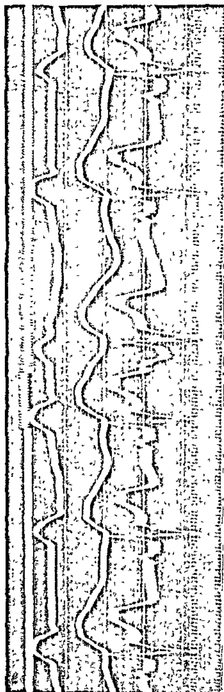


FIG. 31.—From an experiment on a dog Tracings from above downward Signal (stimulation), suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base 0 02 second An auricular extrasystole, elicited by an induction shock, is conducted in a retrograde direction to the sinus node, the post-extrasystolic interval is not compensatory

Fig 31 was obtained from a dog which had been given 0 1 gm of quinine sulphate intravenously a few minutes before the tracing was taken The ventricular cycles measure 0 64 second (rate 93) Owing to the effect of quinine the P-R intervals were lengthened to 0 13 second and the QRS complexes were markedly widened By means of a break *shock applied to an area close to the head* of the sinus node an auricular extrasystole was produced, the P wave of which is seen to have a form similar to those of the sinus beats The post-extrasystolic interval was not compensatory The interval between the P wave of the extrasystole and that of the post-extrasystolic beat measures 0 82 second; this is far too long to be explained by the time required for the extrasystole to reach the pacemaker *in the sinus node, even if full* allowance is made for the slowing effect upon conduction of quinine Inhibition of impulse formation in the sinus node, consequent upon the breaking into it of the extra-stimulus, is the most probable explanation

In man auricular extrasystoles may occur singly, at more or less frequent intervals. In

some cases, one extrasystole follows each normal sinus beat, giving rise to bigeminal heart action or coupled beats; moreover, auricular extrasystoles may occur in succession in shorter or longer groups Like the ventricular complexes in ventricular extrasystoles, the P waves in auricular extrasystoles may maintain the same shape for years A few illustrative cases follow

Fig 32, obtained from a fifty-year-old man without evidence of heart disease, shows auricular extrasystoles after every few sinus beats, in lead 3 they occurred after every sinus beat, producing bigeminal rhythm, due to auricular extrasystoles Except for the extrasystoles the electrocardiogram is normal.

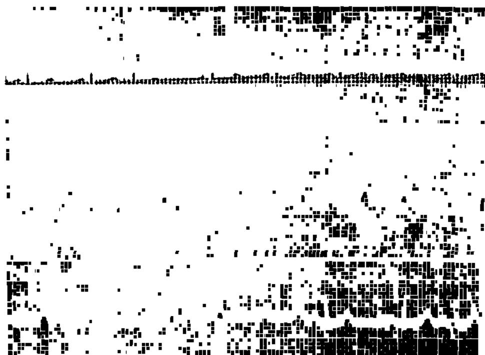
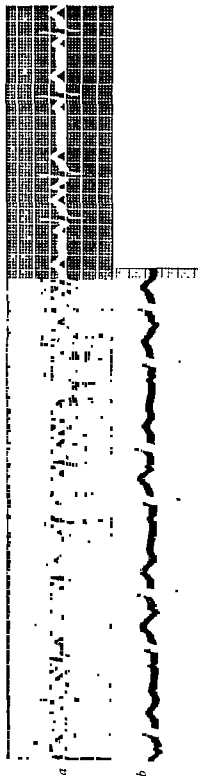


Fig 32.—The three standard leads In leads 1 and 2, one auricular extrasystole after every two or three sinus beats, in lead 3 after every sinus beat

Fig 33 provides an example of multiple auricular extrasystoles occurring in succession three groups each of four are seen to follow a sinus beat This figure also shows another feature often found in electrocardiograms of auricular extrasystoles, namely, the (partial or complete) fusion of the P waves of the extrasystole with the T wave of the preceding beat. It is obvious that the earlier in diastole the extrasystole occurs the more closely its P wave will approximate the T wave of the preceding beat According to the exact time relations of the two waves and their sizes, directions and shapes, the P wave of the extrasystole will produce a more or less marked alteration in the shape of the T wave Such changes usually consist of slurring or notching of the T wave or in an increase or decrease in its height, such alterations clearly indicating the superimposed P wave. If, however, the changes in the T waves are very slight, the recognition of such a wave as containing a P wave may be extremely difficult and in such cases the presence of auricular extrasystoles may easily be missed; this holds good especially for lead 1 in which the normal as well as abnormal P





Auricular bigeminy with alternation in the shape

waves often are very small. An example of very slight changes in T waves caused by blocked auricular extrasystoles is shown in Fig. 40

Auricular extrasystoles, occurring singly, may show varying shape of P waves (*see* Fig 34a) In auricular bigeminy alternation in the shape of the P waves of the extrasystoles is occasionally observed (Fig 34b) These varieties indicate myocardial disease (*see* section on "Prognosis") In cases of myocardial infarction auricular extrasystoles may show typical alterations in their R(S)-T segments which need not be present in the sinus beats This is illustrated by Fig. 35. The auricular extrasystole recorded in lead 2 shows elevation of the R-T junction and pronounced distortion of the R-T segment which features are absent in the sinus beats of this lead (For analogous observations in ventricular extrasystoles, *see* p 31 and Figs 11 and 12)

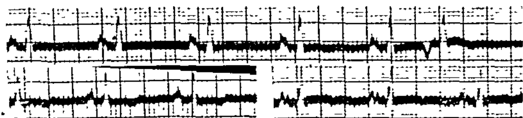


Fig 35—*Top* lead 2, *bottom* leads 1 and 3 From a patient with a recent myocardial infarction The auricular extrasystole in lead 2 shows in its final deflection the high take-off and dome-shaped segment characteristic for the lesion, whereas these features are absent in the final deflections of the sinus beats in this lead These changes may be due to the Ta wave of the inverted P wave

If several auricular extrasystoles occur in succession, the P wave of the first extrasystole may differ in shape from those of the succeeding ones (Fig 44) A similar phenomenon observable with ventricular extrasystoles was described on p 39, its significance is discussed on p 60 Occasionally the shape of the P wave of the last of a series of auricular ectopic beats may differ in shape from those of the others (Fig. 36a) Fig 36b, obtained from a seventeen-year-old patient with rheumatic mitral valvular disease, shows slurred and widened (0 14 second) P waves of the sinus beats, features commonly found in this condition The P wave of the auricular extrasystole is not slurred and measures only 0 10 second

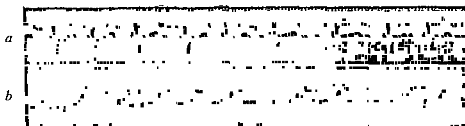


Fig 36—(*a*). Lead 2 Multiple auricular extrasystoles the P wave of the last of which is different in shape from those of the others (*b*) Lead 1. The gross notching and widening noticeable in the P waves of the sinus beats is absent in the P wave of the auricular extrasystole

The Conduction of Auricular Extrasystoles to and in the Ventricles

Auricular extrasystoles which occur late in diastole are, as a rule, normally conducted

to the ventricles; their P-R intervals equal, and their ventricular complexes resemble, those of sinus beats. Auricular extrasystoles of greater prematurity, however, not infrequently exhibit anomalies in auriculo-ventricular and intraventricular conduction; three main types of such disturbances may be distinguished:

1 Delay of atrio-ventricular conduction;
2 Failure of atrio-ventricular conduction: blocked auricular extrasystoles;
3. Aberrant intraventricular conduction

1. Delay of Atrio-ventricular Conduction was seen early in his experimental work by Engelmann in 1894 Since delay in the conduction of the premature auricular contraction results in (1) a lesser degree of prematurity of the ventricular contraction and (2) a shortening of the post-extrasystolic interval (*see* p 47), the arrhythmia becomes less marked in the ventricular rhythm than in the auricular one Engelmann referred to this as an automatic self-adjustment of the ventricular rhythm If the delay in atrio-ventricular conduction of the extrasystole is marked the ventricular contraction may be delayed to such an extent that it occurs almost at the normal time This is often seen in clinical as well as in exprimental work Within certain limits and with certain exceptions (*s below*) the delay in A-V conduction will be the greater the more premature the extrasystole (Hirschfelder and Eyster; Lewis, White and Meakins) The condition is illustrated in Fig. 42

According to Gallavardin the average P-R interval in auricular extrasystoles with inverted P waves in lead 2 was shorter by 0 03 sec. than in those with upright P waves in the same lead This suggests that those with inverted P waves originated near the auricular portion of the A-V node. Some disturbance of the atrio-ventricular conduction was found by him in 50 per cent of fifty cases of auricular extrasystoles

2. Failure of Conduction to the Ventricles of an Auricular Extrasystole results in blocked auricular extrasystoles, that is, premature auricular contractions not followed by a ventricular contraction This condition also was observed early in experimental work (Engelmann 1894, Hering 1901, Trendelenberg 1909) It was first described in man by Hewlett who offered two possible explanations: either the conduction in the A-V system is normal and the failure of a ventricular contraction is due to a disturbance of contractility of the muscle, or conduction is impaired The second explanation seemed more satisfactory to the author and is now generally accepted. Mackenzie attributed the disturbance to the stimulus' reaching refractory tissue on its way to the ventricles This early work was soon confirmed experimentally as well as clinically (Rosenthal, Robinson and Draper, Rihl 1913b) It was found that while the degree of prematurity of the extrasystole is of paramount importance it is by no means the sole decisive factor. Thus the observation is not rare that amongst auricular extrasystoles occurring at the same phase of diastole some are normally conducted whereas others are blocked Variations in vagal tone seem of importance, impaired conduction being found more commonly with a high vagal tone (Robinson and Draper); moreover, periodic changes of excitability (Trendelenburg 1903) and the presence or otherwise of a supernormal phase of conduction (p 497) (Ashman) also pay an important part

In lead 1 the P waves of auricular extrasystoles are often very small (*see* Fig 32) or even absent In the case of blocked auricular premature beats the presence of this arrhythmia may thus be missed if only lead 1 is examined, and the long interval containing a blocked auricular extrasystole without a visible P wave erroneously attributed to depression of the sinus rhythm or to S-A block An instructive example of this kind was reported by Bix (Case 2)

Fig 37a shows numerous auricular extrasystoles characterized by deeply-inverted P waves All occurred at about the same phase of diastole, but some of them were blocked

a

b

Fig. 37.—(a) Conducted and blocked auricular extrasystoles (b) The same, but differing from (a) by great delay in atrio-ventricular conduction



Fig. 38.—Long inhibition of impulse formation in the S-A node after an auricular extrasystole.

whereas others were normally conducted to the ventricles The reason for the differences in conduction in this case is unknown. In Fig. 37b, obtained from another patient, three auricular extrasystoles were blocked whereas two others were conducted to the ventricles, the P-R intervals being lengthened to 0 48 second. (The ventricular complex of the last extrasystole is not reproduced.)

Blocked auricular extrasystoles may exert a profound influence on stimulus formation in the normal pacemaker as well as on the rate of A-V conduction of the following normal beat This suggests that such extrasystoles, though not producing a ventricular contraction, may in certain cases reach the sino-auricular node and be conducted over a certain distance through the A-V conducting system before being blocked This assumption is in accordance with experimental findings in the frog (Engelmann), turtle (Ashman) and dog (Scherf and Shookhoff 1925, Lewis and Master)

The first of these two possibilities is illustrated in Fig 38. After two sinus beats, occurring at an interval of 1 12 second and showing a lengthened P-R interval of 0 28 second, a blocked auricular extrasystole occurred The next P wave followed the extrasystole after the long interval of 1·44 second, the post-extrasystolic interval measuring 2 04 second This very considerable delay in the appearance of the post-extrasystolic beat can only be explained by assuming marked inhibition of the stimulus formation in the normal pacemaker which the blocked auricular impulse must have reached

An extreme example of impairment of atrio-ventricular conduction caused by blocked auricular extrasystoles is provided by Fig 39, obtained from a sixty-four-year-old patient with coronary sclerosis and angina pectoris The first part of the tracing shows sinus rhythm, the P-R intervals being lengthened to 0 28 second The fourth and all subsequent sinus beats were each followed by an auricular extrasystole, all of them blocked, the first one occurring early, the others later in diastole. With the appearance of auricular extrasystoles, conduction of the normal sino-auricular stimuli to the ventricles ceased and complete heart block established itself It must be assumed that the blocked auricular extrasystoles travelled for a certain distance in the A-V system before being blocked and thus further impaired atrio-ventricular conduction to such an extent that conduction became entirely interrupted and complete heart block resulted That blocked auricular beats influence the length of the succeeding A-V interval was found by several investigators (Engelmann 1894, Ashman, Langendorf) Langendorf (Case 1) reported that in this way a subsequent auricular extrasystole may also be blocked

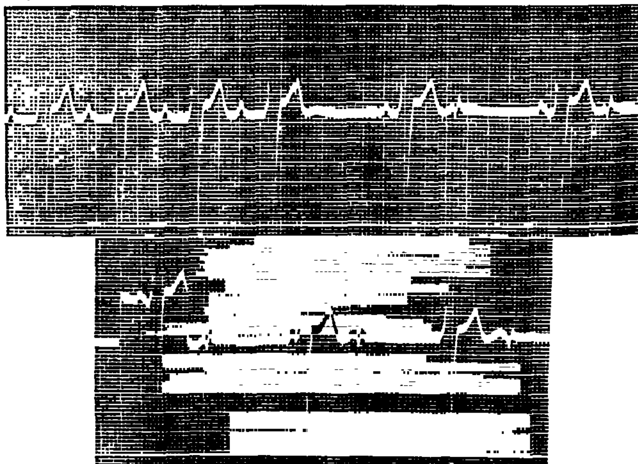
If a blocked auricular extrasystole follows each sinus beat a bradycardia results, the underlying mechanism of which may be difficult to elucidate Even if an electrocardiogram is available the diagnosis may not be easy if the extrasystoles occur early in diastole and their P waves, superimposed on the T waves of the preceding beat, produce only slight alterations of the shape of the latter (*see* p 57) Thus in Fig 40 only a very slight slurring of the T waves indicates that the third, fourth and fifth beats are each followed by a blocked auricular extrasystole In such cases other leads, particularly certain chest (V-1) or oesophageal leads, often are helpful

Large U waves occasionally may be mistaken for blocked auricular extrasystoles Fig. 41 shows both kinds of waves which differed conspicuously from one another by their different shape and direction

3. Aberrant Intraventricular Conduction. As auricular extrasystoles are due to supraventricular impulses which are conducted to the ventricles through the normal pathways it is to be expected that the ventricular complexes resemble those of the sinus beats in a given case While this holds good in many instances (*see* Figs 32, 41), anomalous ventricular complexes associated with auricular extrasystoles, indicating abnormal spread of the impulse through the ventricles, were found soon after the electrocardiographic method had become available for the study of the spread of the excitation wave (Lewis 1910 and 1912

and Rosenthal using one of Lewis's cases). This phenomenon was called " aberration " by Lewis who defined it as " abnormal distribution of the supraventricular impulse in the ventricle " (1925, p 517).

Such abnormalities of the ventricular complexes may be very slight, consisting only of an increase or decrease in the height or depth of one or the other of the waves, or the appearance or disappearance of one of the small (particularly Q) waves In other instances, however, the ventricular portions may be widened, slurred or notched to such an extent that



FIG

they closely resemble ventricular extrasystoles and may easily be confused with them unless due attention is paid to the fact that they are preceded by P waves at intervals usually found with A-V conduction. Confusion with ventricular extrasystoles is particularly apt to occur if the degree of aberration remains the same from beat to beat (which is much less common than a varying degree) or if the premature P wave is buried in the final deflection of the preceding beat Even regular alternation between two forms of aberrant QRS complexes has been described (Stenström, 1923, 1924).



FIG 40 —Blocked auricular extrasystoles causing only very slight changes in the T waves of the preceding beat

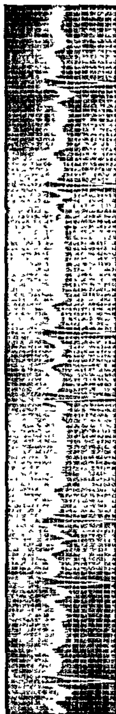


FIG 41 —Lead I Auricular extrasystoles and pronounced U waves

Generally speaking, aberration tends to occur, and to be more marked, the earlier in diastole the extrasystole occurred. It will be seen, however, that other factors also are of importance.

Thus Fig 42, obtained from a twenty-one-year-old woman, shows auricular extrasystoles in each lead In lead 1 on two occasions the P waves of the extrasystoles were fused with the T waves of the preceding beats which they rendered slightly higher and more peaked, the second auricular extrasystole occurred later in diastole and its P wave is very low. In leads 2 and 3 the P waves of the extrasystoles were deeply inverted Aberration of some degree is seen with each extrasystole, but even if extrasystoles occurred in the same phase of diastole the degree of aberration and even the direction of the main deflection of the

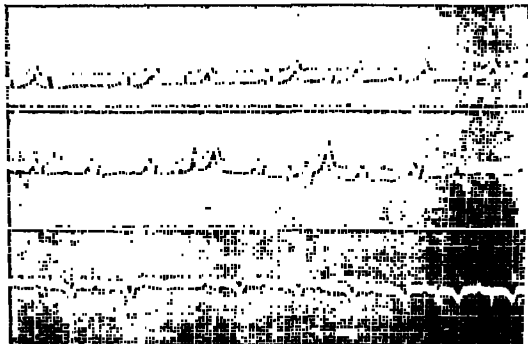


Fig 42.—The three standard leads Auricular extrasystoles with aberrant intra-ventricular conduction The tracings illustrate that this is not solely dependent on the degree of prematurity of the extrasystole For further explanation, see text

ventricular complexes may vary (cf the first and last extrasystole in lead 1 and the second and third in lead 2) Fig 43, reproducing two tracings obtained from the same patient, shows auricular extrasystoles after each sinus beat, some of which were normally conducted, others aberrantly, and others again were blocked Here again the degree of prematurity or length of coupling of the extrasystole to the preceding beat obviously could not have been the sole deciding factors

Experimental and clinical observations have shown that in such cases some other disturbance of conduction, often of a minor degree or even latent, is present.

Experimentally, aberration was found to occur after previous damage of the A-V system (Stenstrom) After slight mechanical damage to the right bundle branch with subsequent recovery of normal conduction, auricular extrasystoles were followed by ventricular complexes of the bundle branch block type Moreover if, at this moment of the

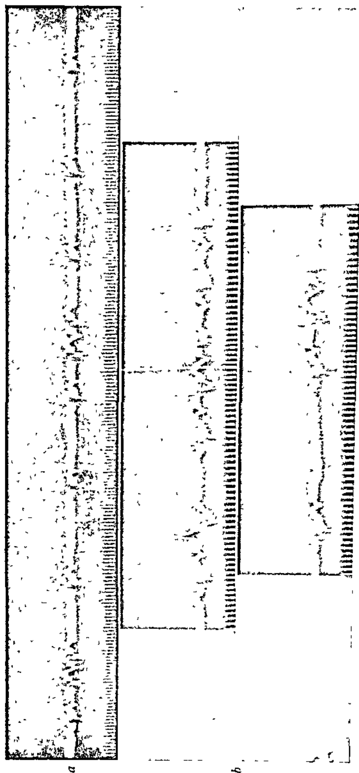


Fig 43 —Auricular extrasystoles, some with normal, some with aberrant intraventricular conduction, and some of them blocked
The middle and bottom strips are continuous

experiment, the conducting system was fatigued by a series of ventricular extrasystoles produced in rapid succession, the following sinus beats temporarily showed the features of right bundle branch block (Scherf, 1927). Lewis (1925) found that beats of this kind could be obtained more easily in the cat, when the heart presented slight changes of conduction, for instance during asphyxia.

Fig 43 illustrates another observation which is by no means rare, namely, that the first of a series of auricular extrasystoles shows a particularly delayed conduction and marked degree of intraventricular aberration Thus in Fig 43a one blocked auricular extrasystole followed each normal beat except for two occasions when two conducted extrasystoles occurred in succession The first extrasystole of each of these two groups showed a delayed A-V conduction of 0 24 second, followed the preceding beat after 0·44 second, and their ventricular complexes showed marked aberration. The second extrasystole of each group, which was conducted at a normal rate to the ventricles, followed the preceding beat (the first extrasystole of the group) at an interval of only 0·36 second, and their ventricular complexes showed less aberration Similar conditions are shown in Fig. 43b, in the second *half of which an auricular extrasystole with delayed A-V conduction and a coupling of 0·42* second was aberrantly conducted, whereas the succeeding one, following after only 0·34 second with a normal P-R interval, had an almost normal ventricular complex (*see* also Figs 57a and 58 in the section on A-V extrasystoles)

These observations, which tend to prove that the degree of prematurity cannot be the sole decisive factor to account for the presence or degree of aberrant intraventricular conduction, at first sight are surprising in another respect One would expect that with a succession of extrasystoles the degree of disturbance of conduction, both atrio-ventricular and *intraventricular, would gradually increase, whereas the records clearly show the first* extrasystole to be most affected in this respect. Moreover, it is by no means rare that, also with longer series of auricular extrasystoles, the first one displays particularly marked delay in A-V conduction and degree of intraventricular aberration Similar observations were made in cases of periodically dropped beats (Scherf, 1929). Another observation relevant in this connexion is that in a series of ventricular extrasystoles the first one may be different from the others in the electrocardiogram (*see* Fig 21), or, more rarely, in a series of auricular extrasystoles the shape of the P wave of the first one may differ from that of all subsequent ones (Fig 44, lead 2)

Consideration of the refractory phase seems to afford the explanation. It has been established that the refractory period shortens as a result of increased heart rate (Trendelenburg, 1903; Mines, Lewis, Drury and Bulger) and of fatigue (Adrian) and the refractory period of a premature contraction was found to be shorter than that of a beat occurring after a longer interval (Trendelenburg 1903, Junkmann). (*See* also section on "Dynamics and Refractory Period") The assumption seems justified, therefore, that beats occurring after long intervals (for instance the sixth beat of Fig 43a which was a post-extrasystolic beat after a long post-extrasystolic interval) have a long refractory period so that an extrasystole *following on such a beat will find the tissue only partially recovered; the disturbed conduction* resulting from partial refractoriness (Lewis, 1925) will account for delayed A-V as well as for aberrant intraventricular conduction The extrasystole itself, having a shorter

[1] Other factors of importance in this connexion are toxic damage of the heart, for example by quinidine, which tends to make aberration more pronounced (Berliner and Lewithin), and vagal tone Since stimulation of the vagus is known materially to shorten the refractory period of the dog's auricle and thereby indirectly to improve conduction of impulses falling within the period of recovery from a preceding beat, variations of vagal

tone may well account for the different behaviour of auricular extrasystoles occurring in man under otherwise seemingly identical conditions Since there is no evidence of a direct action of the vagus on the mammalian ventricle the intraventricular conduction is not influenced directly by a change in vagal tone

Reports about the incidence of aberrant conduction of auricular extrasystoles give varying figures: White and Stevens found it in eleven out of twenty-three cases, Palmer and

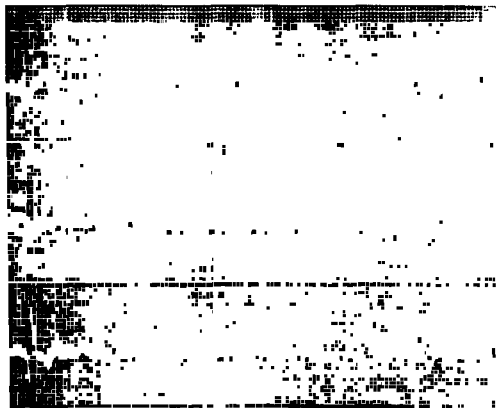


Fig 44 The three standard leads The record [illegible]

White saw it 107 times in a series of 387 cases, in a more recent series of fifty cases it [illegible]

If successive auricular extrasystoles follow one another at irregular intervals differentiation from auricular fibrillation can only be made electrocardiographically Fig 36a illustrates this condition, showing, moreover, the extrasystoles to have varying P-R intervals

Occurrence of Heterotopic Beats following an Auricular Extrasystole

Just as in the case of ventricular extrasystoles, the post-extrasystolic interval following



Fig 45 —Blocked auricular extrasystoles followed by an escaped beat.

auricular extrasystoles may be terminated by an escaped beat originating in a centre other than the normal pacemaker Escape of a lower centre is particularly apt to occur after blocked auricular extrasystoles, as here the post-extrasystolic interval tends to be particularly long. Fig. 45 shows a blocked auricular extrasystole occurring after each group of two normal beats, the post-extrasystolic interval being invariably terminated by an escaped beat originating in the A-V node. (The normal P wave of the sinus beat due to occur shortly after the escaped beat is visible between the QRS complex and T wave of the escaped beats)

In other instances the post-extrasystolic interval is terminated by supra-ventricular beats showing abnormal P waves. Thus Fig 46a, taken from a patient with rheumatic mitral valvular disease, shows widened and notched P waves. The two beats following an auricular extrasystole exhibit different and grossly abnormal P waves. The post-extrasystolic interval is not compensatory Such abnormal P waves of beats following an auricular extrasystole usually have the same shape as that of the extrasystole (observed also in oesophageal leads, Enselberg), but exceptions occur In Fig 46b the auricular extrasystole had a distinctly positive P wave, whereas the P waves of the three following beats were very low and gradually increased in height. Intra-auricular disturbances of conduction may also play a part The same phenomenon could frequently be observed in experiments on dogs (Rothberger and Scherf).

Usually this phenomenon is transitory and only found in the first few post-extrasystolic beats. The post-extrasystolic interval tends to be equal to, or slightly shorter than, that found without alterations of the P waves of the post-extrasystolic beats.

In his first description of this phenomenon Lewis (1912) pointed out that the discharge of the abnormal extrasystolic impulse may precipitate formation at the same site of the next impulse to be discharged at the time it is due This view is supported by the experimental observation that following rhythmical stimulation of the auricle the first impulse after the end of stimulation may arise in the stimulated area and not the normal pacemaker (Skramlik, Rachmilewitz and Scherf, Bloch) Abnormal centres other than the centre of origin of the extrasystole also may temporarily give rise to impulses after the post-extrasystolic interval

Post-extrasystolic beats following auricular extrasystoles, whether blocked or conducted, may show the same kind of alterations of T waves as were described regarding those following ventricular extrasystoles (p 37).

Differentiation between Blocked Auricular Extrasystoles and 2 : 1 A-V Block

It is well known that in 2 : 1 A-V block those P-P intervals which contain a conducted beat often are shorter than those without it, the P wave following a ventricular complex occurring slightly prematurely as compared with the subsequent P wave. Moreover, the

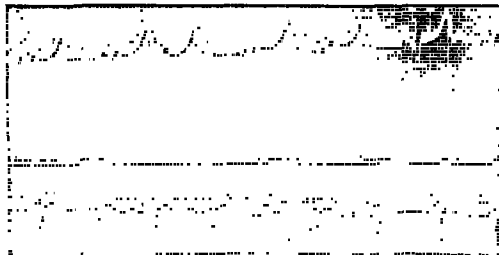


Fig. 46.—Both tracings lead 1, from different patients. Changes in the shape of the P waves of the first few post-extrasystolic sinus beats after an auricular extrasystole. For further explanation, see text.

premature P waves in 2 : 1 A-V block may differ in shape from the others (Scherf, 1945). This sequence—a conducted beat followed by an isolated premature P wave of different shape obviously would fit both with a diagnosis of blocked auricular extrasystoles and that of 2 : 1 A-V block, and special measures may be necessary to arrive at a differential diagnosis, the clinical importance of which is considerable. Fig. 47, obtained from an eighteen-year-old patient with rheumatic fever, provides an example. It shows conducted beats, the P-R intervals being lengthened to 0.24 second, followed by slightly premature P waves which

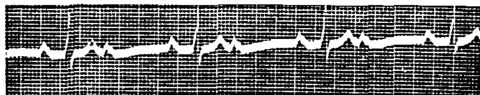


Fig. 47.—Lead 2. 2 : 1 A-V block simulating blocked auricular extrasystoles.

degree (say, 3 : 1) and the differential diagnosis will be made possible in this way. Other tracings of the same patient revealed that actually 2 : 1 A-V block was present in Fig. 47.

[The mechanism underlying the changes in the time relations and shape of P waves in 2 : 1 block is not fully understood, periodical changes in vagal tone are the most likely explanation, each pulse wave following a ventricular contraction producing a temporary increase in vagal tone via the pressor-receptor nerves (Erlanger and Blackman, Ashman and Gouaux, Scherf, 1945).]

Combination of auricular and ventricular extrasystoles in the same patient

This combination of ectopic beats is occasionally observed, but is not very common. Figs. 48 and 49 provide examples.

Fig. 48, obtained from a sixty-six-year-old man with hypertension, shows also the unusual feature that a ventricular extrasystole mostly occurred immediately after an auricular one (top record), but this was not invariably the case as illustrated in the bottom record.

Fig. 49, recorded in a twenty-three-year-old man with attacks of paroxysmal tachycardia while on a preventive maintenance dose of quinidine, shows in its middle portion auricular bigeminy. The third beat is an auricular extrasystole with gross aberration of intra-ventricular conduction. Its P wave is recognizable as a notch in the ascending limb of the preceding T wave (R-P = 0.4 second, P-R = 0.26 second as compared with the R-P of 0.48 and P-R of 0.16 second of the extrasystoles of the bigemini with normal intra-ventricular conduction). The penultimate beat is a ventricular extrasystole. The disturbances in intra-ventricular conduction of the sinus beats are attributable to quinidine.

Fig. 44 may be another instance, showing ventricular extrasystoles in lead I and auricular ones in leads 2 and 3 though the ectopic beats in lead 1 may be auricular in origin with aberrant intraventricular conduction. Such possibility has to be considered particularly as the P waves of auricular extrasystoles are often very small or absent in lead I.

According to Huppert and Berliner the occurrence of both auricular and ventricular extrasystoles is strongly suggestive of cardiac disease. In one series of these authors all the twenty-five patients, in whom this combination was encountered, were suffering from cardiac disease. In another series of twenty-one cases, in whom sinus tachycardia (rate 100 and over) was present in addition, only two patients were free from cardiac involvement.

SUMMARY

Three main varieties of disturbances of rhythm caused by auricular extrasystoles are distinguished and illustrated diagrammatically: auricular premature beats without, and with conduction of the ectopic impulse to the S-A node and therefore without, and with shifting of the dominant rhythm, and blocked auricular extrasystoles. The numerous and complex factors determining the length of the post-extrasystolic interval in the ventricular rhythm are discussed and analysed.

The electrocardiogram of auricular extrasystoles is described in detail under three main headings.

A. Shape of the P waves, including some special features, such as bigeminal rhythm due to one auricular extrasystole following each sino-auricular beat, diagnostic difficulties arising out of the superposition of small P waves on the T of the preceding beat, and peculiarities of the P waves in auricular extrasystoles occurring in succession.

B. Conduction of auricular extrasystoles to and in the ventricles. Three main aspects of this are discussed.

(1) Delay of A-V conduction. It is pointed out that, while the degree of prematurity is the most important factor in determining the length of the A-V conduction time of an

Fig. 48.—Lead aVR The two strips are continuous Auricular and ventricular extrasystoles For further explanation, see text

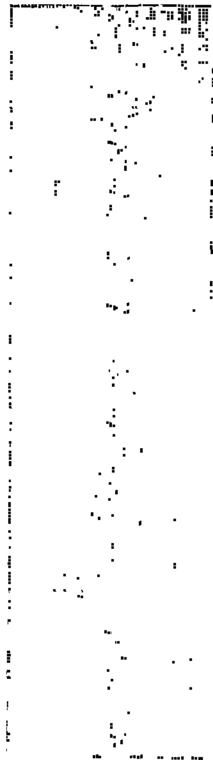


Fig. 49.—Lead V-2 Auricular and ventricular extrasystoles For further explanation, see text

auricular extrasystole, this is not the only one and others, discussed under (2), have to be considered

(2) Failure of conduction to the ventricles of an auricular extrasystole: blocked auricular extrasystoles. While the degree of prematurity of the ectopic beat is the most important factor determining whether or not the impulse reaches the ventricles, variations in vagal tone, changes in excitability of the ventricles and the presence or otherwise of a supernormal phase of conductivity also play an important rôle. Blocked auricular extrasystoles may exert a profound influence on impulse formation in the S-A node and on the rate of A-V conduction; this is illustrated by clinical examples

(3) Aberration of intra-ventricular conduction This tends to occur, and to be more marked, the earlier in diastole the extrasystole

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this is absent, is explained by the length of the refractory period preceding the first, and the subsequent beats respectively of such series. Other factors are toxic damage to the heart and variations in vagal tone in the auricles

C The occurrence of heterotopic beats occurring after an auricular extrasystole and terminating the post-extrasystolic interval. Several varieties of such beats are discussed and their

auri

Instances of a combination of auricular and ventricular extrasystoles in the same patient are described

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ATRIO-VENTRICULAR EXTRASYSTOLES

Introductory Remarks

Extrasystoles originating in the atrio-ventricular (A-V) node were first described by Pan and by Volhard, both in 1904 before the discovery of the A-V node, but misinterpreted as ventricular extrasystoles with retrograde conduction to the auricles In the same year Mackenzie published the tracing of an A-V extrasystole which, however, is not described as such In 1906, extrasystoles originating in the A-V node in monkeys were described by Hering and considered to have been due to increased resistance to the emptying of the left ventricle The first clinical examples of this arrhythmia were those of Hering and Rihl (1906), Ritchie (1907) and Mackenzie (1908) Subsequently cases were described by Lewis, Wenckebach and Winterberg, and others

The diagnosis of A-V extrasystoles and our conception about their site of origin within the A-V node as well as their mode of conduction are based on our knowledge of A-V nodal rhythm.

The origin of the impulse in the A-V node results in the spread of the excitation wave through auricles and ventricles in such a way that their contraction occurs more nearly simultaneously than with any other site of origin of impulse formation Moreover, while the direction of the spread of the excitation wave through the ventricles is the same as that of beats of supraventricular origin, in the auricles it is the reverse By studying the curves of the momentary electrical axes (vectors) in A-V nodal rhythm Ruskin and Decherd found them to pass upwards, backwards and to the left as compared with a downward and forward course to the left in sinus rhythm.

Upper, middle and lower A-V rhythm and A-V extrasystoles

A-V rhythm and A-V extrasystoles were further subdivided according to whether activation of the auricles precedes, coincides with, or follows that of the ventricles In the electrocardiogram these three groups are characterized by the position of the P waves in relation to the QRS complexes, the P waves preceding, coinciding with, or following the QRS complexes respectively

For a considerable time in the past the position of the P waves in relation to the QRS complexes was taken to indicate the site of origin within the A-V node of such beats This view was based on the results of the early experiments of Ganter and Zahn, and of Zahn, [illegible] ventricular contraction, of warm- [illegible] [illegible]d Eyster's experiments on the site [illegible] This interpretation was accepted by Clerc and Pezzi, Wenckebach and Winterberg (pp. 143, 199) and others For different reasons Lewis, though he considered " the exact location of events in a small structure buried under septal muscle " " precarious ", believed it to be correct

This conception, some suggested modifications of which will be discussed below, is diagrammatically illustrated in Fig 50 In Fig 50a origin of the A-V beat in the upper (auricular) portion of the A-V node is assumed. As the centre of impulse formation lies nearer to the auricles than to the ventricles and the A-V node is known to delay the propagation of the impulse, the auricles are activated before the ventricles; and in the electrocardiogram a P wave precedes the QRS complex with a more or less shortened P-R interval With the impulse originating in the middle portion of the A-V node (Fig. 50b), the con- [illegible]

thus buried in it If the impulse originates in the ventricular portion of the A-V node, as shown in Fig. 50c, the auricles will be activated later than the ventricles and the electrocardiogram will show a negative P-R (or an R-P) interval, a P wave following the QRS complex.

The Electrocardiogram

General Features

These considerations about the direction of spread of the excitation wave and the sequence of auricular and ventricular activation explain the electrocardiographic features in the different varieties of A-V extrasystoles

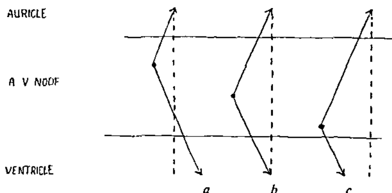


FIG 50 —Diagram illustrating the three varieties of A-V rhythm and/or A-V extrasystoles

In the standard limb leads they are characterized by premature ventricular complexes of supraventricular shape,

(a) which are preceded or followed by P waves which are low positive or iso-electric in lead 1 and sharply inverted and often peaked in leads 2 and 3,

or

(b) in relation to which separate P waves are absent

In those forms of (a), in which a P wave precedes the ventricular complex, the P-R intervals are often abnormally short. In the variety (b) the P wave, being inscribed simultaneously with, and buried in, the QRS complex often produces some alteration in the shape of the latter

In the augmented unipolar right arm lead aVR the P waves of A-V beats are upright (whereas those of sinus beats are inverted in this lead), in the unipolar left leg lead aVF A-V beats show inverted P waves (*see* Fig 58)

Fig 51, obtained from a seventy-five-year-old woman with coronary sclerosis, reproduces A-V extrasystoles with preceding activation of the auricles One extrasystole is seen in lead 1, showing a low upright P wave Two extrasystoles are seen in leads 2 and CR-4 respectively and one in lead 3, all showing deeply inverted P waves and P-R intervals shortened to 0 08 second as compared with the 0 13 second of the sino-auricular beats The presumed site of origin of the extrasystoles is the auricular portion of the A-V node The

Fig. 52 provides an example of an A-V extrasystole with simultaneous activation of auricles and ventricles. After three sinus beats a premature ventricular complex, having almost the same shape as those of the sinus beats, was recorded in connexion with which no P wave is visible The post-extrasystolic interval was compensatory Since in relation to such premature contractions P waves were also absent in all other leads, simultaneous activation of auricles and ventricles has to be assumed Close inspection of the QRS complex of the extrasystole shows that the R wave is smaller and the S wave deeper than the corresponding waves of the sinus beats. These differences have to be ascribed to the presence of an inverted P wave buried in the QRS complex In order to be certain that auricles

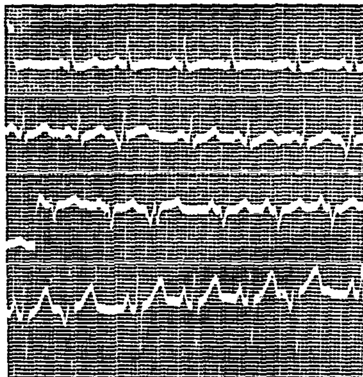


Fig [illegible]

shortened

and ventricles contracted simultaneously a record of the venous pulse is necessary in which an A-V extrasystole manifests itself by a premature high wave consisting of the auricular *a* wave superimposed on the ventricular *c* wave. In such cases the extrasystole is believed to originate in the middle portion of the A-V node

Figs 53 and 54 provide examples of A-V extrasystoles with preceding activation of the ventricles, presumed to originate in the ventricular portion of the A-V node

Fig. 53, obtained from a forty-eight-year-old healthy woman, shows a premature ventricular complex of supraventricular shape after which a shallow inverted P wave is visible between the QRS and T waves. The post-extrasystolic interval was not compensatory.

In Fig. 54 two A-V extrasystoles in each of the three leads are seen, the P waves following the QRS complexes being very shallow in lead 1 and sharply inverted in leads 2 and 3. The post-extrasystolic intervals were not compensatory and the intervals between the inverted P waves of the extrasystoles and the P waves of the next S-A beats were slightly longer than those between two sinus beats These time relations are reminiscent of those in ventricular extrasystoles in complete A-V block and are most likely due to the same mechanism: destruction of the immature impulse in the centre of the dominant rhythm by the extrasystole with slight inhibition of impulse formation

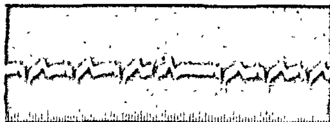


FIG 52—Lead 2 A-V extrasystole with simultaneous activation of auricles and ventricles, presumably originating in the middle portion of the A-V node The P wave of the extrasystole is buried in its QRS complex

In cases with preceding activation of the ventricles the P wave of the extrasystole may occasionally show every intermediate form between being sharply inverted in leads 2 and 3, as described, and that of normal sinus beats This is due to interference between the retrograde activation of the auricles from the extrasystolic focus and the orthograde one from the sino-auricular node This phenomenon will only be observed in extrasystoles occurring very late in diastole, at a time when the next normal impulse is due

The length of the post-extrasystolic intervals after A-V extrasystoles depends on the same factors as that following auricular ones and may be compensatory or shorter than compensatory No data are available as to which of these two varieties is commoner.



Fig 53—Lead 3 A-V extrasystole with preceding activation of the ventricles, presumably originating in the lower portion of the A-V node Its inverted P wave is visible between the QRS complex and T wave

Coronary sinus rhythm and coronary sinus extrasystoles

Attempts have been made (Zahn, Scherf and Harris, Michaelides and Costeas) to separate from a rhythm originating in the upper portion of the A-V node, and showing inverted P waves in leads 2 and 3 with a *shortened* P-R interval, another form in which the [illegible]

Scherf, 1944) and records obtained in the dog of beats produced by stimulating this area

show the same features as tracings which are relatively common in man. (In our opinion this type of A-V rhythm is commoner than all the other types and has frequently been misinterpreted in clinical electrocardiography.) Extrasystoles showing the form of P waves in the different leads as described above and associated with a normal P-R interval should therefore be called "coronary sinus extrasystoles".

It is, however, not possible to separate coronary sinus extrasystoles from upper nodal A-V ones with any degree of certainty because the length of the P-R interval of such beats, on which the distinction has to be based, is profoundly affected by disturbances of conduction This is discussed below.

The term "coronary sinus rhythm" was also applied, in our opinion erroneously, to a type of tracing showing normal P waves with shortened P-R intervals (Katz) We believe that such tracings do not indicate an ectopic site of impulse formation, but sinus rhythm

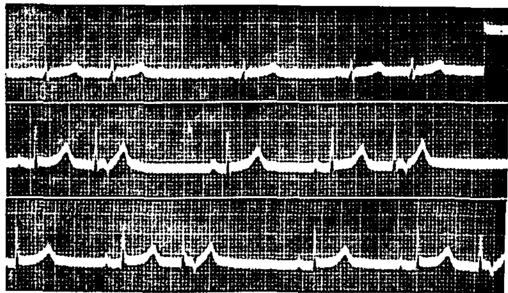


FIG 54 —The standard leads A-V extrasystoles with preceding activation of the ventricles, presumably originating in the lower portion of the A-V node

which, in certain conditions (left ventricular strain in certain types of hypertension, vitamin B_1 deficiency), may be associated with a shortened P-R interval (Scherf, 1941) The use of the term "coronary sinus rhythm" for this kind of record does not appear to be justified and, since it also tends to confuse the issue, should be discouraged

The effect of disturbances of conduction upon the electrocardiogram of A-V extrasystoles

While a more detailed review of the conditions influencing the electrocardiogram in cases of A-V rhythm is outside the scope of this book, it may be said that some objections have been raised as to the validity of the scheme on which our discussion of the various types of A-V rhythm and A-V extrasystoles has been based Such objections are mainly founded on the following observations: The position of the P waves in relation to the QRS complexes is determined, not only by the site of impulse formation within the A-V node, but also by the rate of conduction of the impulse into the auricles and ventricles respectively, slight changes of which may produce marked alterations in the P-R or R-P intervals in A-V rhythm Moreover, intra-auricular disturbances of conduction may profoundly affect the

shape of the P waves in A-V rhythm (Scherf and Shookhoff, 1926) and sinus rhythm (Rothberger and Scherf)

A few examples. Temporary disturbances of conduction in the bundle of His may produce a temporary lengthening of the P-R intervals, though the centre of impulse formation remains unchanged in the lower portions of the A-V node (Scherf and Shookhoff, 1925), inverted P waves with normal P-R intervals do not necessarily exclude an origin of the extrasystole in lower parts of the A-V node as they may be the result of delay in conduction (Scherf, 1931, *see also* diagrammatic illustration of Fig 55, and section on the influence of extrasystoles on A-V rhythm, p 102), upper nodal (and coronary sinus) rhythm may be associated with P-R intervals exceeding 0 12 second, the length of this interval being sometimes, but not invariably, related to the length of the P-R interval of the sinus beats in the same patient (Scherf and Harris), also, in experimental coronary sinus rhythm in the dog P-R intervals exceeding 0 12 second were occasionally observed (Scherf, 1944).

This view has been accepted by others. For instance, Langendorf, Simon and Katz believe that sharply inverted P waves in leads 2 and 3 with P-R intervals exceeding 0 12 second indicate A-V rhythm with A-V block rather than sinus rhythm with intra-auricular disturbances of conduction In our opinion this is usually coronary sinus rhythm

A further degree of disturbances of conduction is the complete blocking of the impulse of an A-V extrasystole in one or other direction. Instances of blocked conduction to the

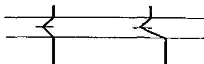


Fig 55 —Diagram illustrating the effect in A-V rhythm, upon the position of the P wave in relation to the QRS-T complex, of disturbances of conduction in the A-V system

ventricles were published by Dack and Mond, and by Holzmann (p 465) In the first-mentioned case two coupled extrasystoles occurred at times The venous pulse tracing, taken in addition to the electrocardiogram, proved both beats to have been of A-V origin, though only one of them produced an inverted P wave, whereas the other showed simultaneous activation of auricles and ventricles P waves were visible only when, owing to block in the ventricles, no QRS complex was inscribed—an instructive example of the importance of disturbances of conduction in determining the features of A-V extrasystoles in the electrocardiogram

Langendorf and Mehlman described a case in which A-V extrasystoles with blocked conduction to auricles as well as to ventricles could be diagnosed with a great degree of probability Obviously, with conduction blocked in both directions, such extrasystoles could not give rise to either auricular or ventricular waves in the electrocardiogram, but their presence could be deduced by the disturbance of the sinus rhythm which they caused. This consisted in, either a sudden lengthening of the P-R interval of the following sinus beat, or a dropped beat without any preceding increase of the P-R interval A similar observation, concerning interpolated A-V extrasystoles, was described by Bix (Case 1)

Revised classification of the various types of A-V rhythm and A-V extrasystoles

In view of such observations, it has been thought that it is no longer permissible to distinguish an upper, middle and lower nodal rhythm according to the position of the P waves in relation to the QRS complexes Instead, it has been proposed that this classification should be replaced by distinguishing A-V rhythm (and A-V extrasystoles) (a) with preceding

auricular, (b) with simultaneous auricular and ventricular, and (c) with preceding ventricular activation (Holzmann, p 460). While we do not intend to pronounce any final judgment as to the extent to which it is possible to deduce from electrocardiograms the site of origin within the A-V node of impulses in A-V rhythm and A-V extrasystoles, in our opinion such a determination is possible with a fair degree of probability at least as far as a distinction between impulse formation in the upper (including coronary sinus area) and lower portions of the A-V node is concerned. This view is also supported by the differences in anatomical structure of the various portions of the A-V node (Kung), and by the absence, in a large proportion of cases, of any signs of disturbances of conduction. A distinction between coronary sinus and upper nodal rhythm is not possible with any degree of certainty, as already referred to

A-V extrasystoles with upright P waves in leads 2 and 3

In the dog, upright P waves in A-V rhythm can be found in the ano-oesophageal lead (closely corresponding to lead 3), particularly in instances of altered intra-auricular conduction due to certain poisons (Scherf and Shookhoff, 1926)

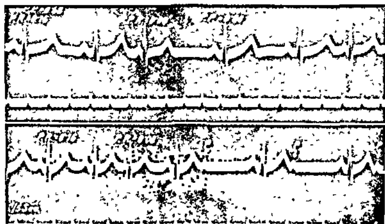


FIG 56 —Top tracing lead 1, bottom tracing lead 2 A-V extrasystoles with upright P waves, some with blocked ventricular conduction From McGUIRE and ROSENBERGER *Z Kreisl Forsch*

Electrocardiograms in man showing A-V rhythm with upright P waves in leads 2 and 3, preceding QRS complexes of normal supraventricular shape with shortened P-R intervals, are rare, but the few clinical records of this kind which have been published can best be explained by the assumption of an A-V origin of such rhythms (Holzmann and Scherf) The most convincing case in which such beats occurred as extrasystoles is the one reported by McGuire and Rosenberger from whose paper Fig 56 is taken In the upper tracing two normal sinus beats with a P-R interval of 0 16 second and with rounded P waves are followed by a premature beat with a P-R interval of 0 08 second, the P wave of which was also upright, but had a different, more pointed shape The ventricular complex of this beat resembled those of the sinus beats except for being slightly higher After another two sinus beats, a premature beat with the same features occurred Longer tracings made it possible to exclude interference between sino-auricular and atrio-ventricular rhythm, and auricular extrasystoles could be ruled out by the shortened P-R intervals. A-V extrasystoles seems the correct explanation The lower tracing shows that conduction to the ventricles of such premature beats was blocked if they followed the preceding beat with a shorter

coupling; in such instances, isolated P waves were recorded after the T waves of the preceding beat In both tracings the intervals following the extrasystoles were not compensatory and the intervals between the extrasystolic and post-extrasystolic P waves equalled that between two normal sinus beats

Multiple A-V extrasystoles

Occasionally A-V extrasystoles occur in succession, forming shorter or longer groups In the electrocardiogram such ectopic beats show ventricular complexes of supraventricular form, preceded by P waves which are inverted in the leads discussed above, and having shortened P-R intervals

Fig 57a shows an example of two such series, interrupted by one normal sinus beat The P-R intervals of the extrasystoles measure 0 12 second as compared with the 0·17 second of the sinus beat The first extrasystole of the second series shows marked aberration of the ventricular complex and its P-R interval is longer (0·2 second) than that of the other extrasystoles The factors responsible for disturbances of conduction affecting the first of a series of extrasystoles were discussed in connexion with those of ventricular and auricular origin (*see* pp 39 and 60) Such extrasystoles in groups form a transition to short runs of paroxysmal tachycardia An example of this in which exercise increased the rate of the A-V tachycardia is discussed in the section on paroxysmal tachycardia (Scherf and Weissberg, *see* p 237)

Fig 57b reproduces a group of nine A-V extrasystoles with preceding activation of the auricles, presumably originating in the upper part of the A-V node The whole paroxysm is shown, including sinus beats before and after it The P-R interval of the sinus beats was 0 20 second, that of the A-V beats 0 16 second The first A-V beat occurred prematurely, the last was followed by a post-extrasystolic interval

Fig 58 was obtained from a young



Fig 57.—Both tracings lead 2, obtained from different patients Multiple A-V extrasystoles (short paroxysms of A-V tachycardia)

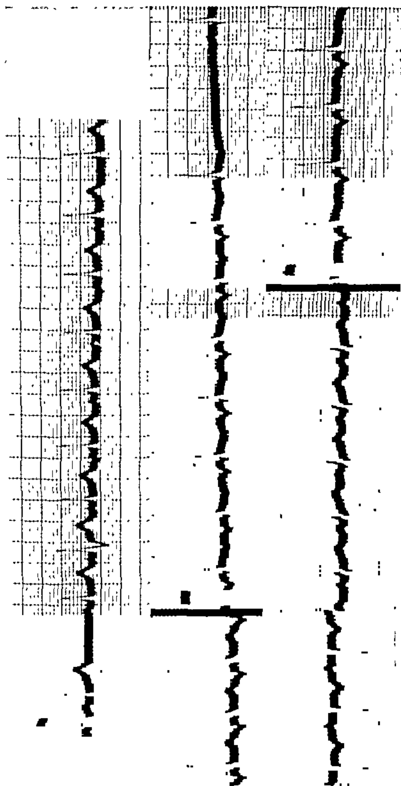


FIG. 58.—Top tracing: lead I, middle, leads 2 and 3, bottom, leads aVR, aVL and aVF. Multiple A-V extrasystoles

man without any evidence of structural heart disease Lead 1 shows a paroxysm of supraventricular tachycardia with aberration of the first extrasystole The deep, sharply inverted P waves in leads 2, 3 and aVF and the upright P waves in leads aVR and aVL strongly suggest that the ectopic beats originated in the A-V node

Fig 59 illustrates the unusual combination of a coronary sinus and a ventricular extrasystole

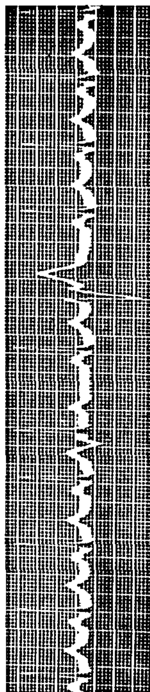


Fig 59 —Lead 2. Combination of a coronary sinus and a ventricular extrasystole

Clinical significance

A-V extrasystoles are rare Not infrequently they are erroneously diagnosed in cases of auricular extrasystoles whose P waves are indistinct or buried in the final deflection of the preceding beat

A-V extrasystoles have the same significance as ventricular and auricular ones Since in the A-V variety the flow of blood from auricles into ventricles is more seriously impaired than is the rule with the two other types, it results in a larger quantity of blood being thrust back into the veins which, in some patients, gives rise to a particularly unpleasant kind of palpitation

SUMMARY

Our conceptions about the site of origin within the A-V node and the diagnostic criteria of A-V extrasystoles are based on observations on A-V rhythm It is pointed out that, with the impulse arising in the A-V node, the contraction of auricles and ventricles occurs more nearly simultaneously than with any other site of impulse formation A-V rhythm and A-V extrasystoles were subdivided according to whether activation of the auricles precedes, coincides with, or follows that of the ventricles The foundation of the view is briefly stated that these different sequences of activation indicate origin of the impulse in the upper, middle or lower portions of the A-V node respectively The mechanism of these three varieties is diagrammatically illustrated The electrocardiographic features of the several kinds of A-V extrasystoles are discussed and illustrated by examples The attempts at separating a coronary sinus rhythm from upper nodal A-V rhythm are critically discussed and it is concluded that such distinction is not possible with any degree of certainty This is due to the effect of disturbances of conduction upon the electrocardiogram of A-V extrasystoles which is discussed in some detail, including reports of cases of A-V extrasystoles with blocked conduction to auricles as well as to ventricles The complicating factors introduced by disturbances of conduction have resulted in doubts about the possibility of deducing from the electrocardiographic features the site of origin within the A-V node of A-V beats A suggested revised classification is discussed which distinguishes A-V rhythm and A-V extrasystoles (a) with preceding

auricular, (b) with simultaneous auricular and ventricular, and (c) with preceding ventricular activation.

While we do not intend to offer any final opinion on this subject, reasons are given for our view that a distinction between impulse formation in the upper (including coronary sinus area) and lower portions of the A-V node is possible with a fair degree of probability.

Instances of A-V extrasystoles in groups (multiple A-V extrasystoles) are described. The clinical aspects of this arrhythmia are briefly discussed

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SINUS EXTRASYSTOLES

It is a well recognized fact that, in the mammalian heart, centres with the highest degree of spontaneous impulse formation are least prone to produce extrasystoles and vice versa. The commonest site of origin of extrasystoles are the ventricles, which have the lowest automaticity Conversely, the S-A node which, owing to its high rate of impulse formation, is the normal pacemaker of the mammalian heart gives rise to extrasystoles so rarely that only a very few cases are on record in which the presence of sinus extrasystoles in man can unreservedly be accepted

On the grounds of the time relations in polygraphic tracings this arrhythmia was first reported in man by Wenckebach in 1907 and Rihl in 1913

Experimental Observations

Experimentally, the extra-contractions elicited from the sinus and the great veins have been studied on numerous occasions, and some particular properties were found which are of physiological as well as of clinical interest

One of the earliest investigations is that of Tigerstedt and Stromberg who in 1888 found on the blood-filled sinus venosus of the frog's heart that the post-extrasystolic interval was not compensatory, as had been established for the ventricle by Marey, but often shorter Owing to the smallness of the recorded excursions obtained with a primitive method no finer analysis of the time relations was possible. In his classical investigations on the frog's heart Engelmann (1896) established beyond doubt that the interval following an extrasystole originating in the sinus or the great veins as a rule equalled the interval between two normal contractions With extrasystoles occurring early in diastole the post-extrasystolic interval often was longer than that between two normal beats, but with cycle lengths of one to three seconds this lengthening never exceeded 0 2–0 3 second, and in fifteen thousand instances observed in over a hundred frogs never reached the degree of making the pause compensatory The later in diastole the extrasystole occurred the smaller the increase in length of the post-extrasystolic interval, the moment in diastole in which an extrasystole was followed by an interval equalling the normal cycle length varied in different instances Occasionally the post-extrasystolic interval was slightly shorter than the interval between two normal beats.

The problem was recently re-examined by Emery and Loomis (1943) in the heart of the tortoise By means of a fine thread and carefully equilibrated aluminium lever, mechanical records of the beating sinus were obtained and over two thousand tracings analysed. While the fundamental fact was confirmed that the post-extrasystolic intervals following sinus extrasystoles were never compensatory, some details regarding their length were found to differ from those prevailing in the frog's heart If the extra-contraction was produced within the first quarter of the cycle the post-extrasystolic interval was always shorter than a normal cycle length, if it originated in the first third of the cycle the post-extrasystolic interval was shorter than the period between two normal beats in 77 per cent and longer in 9 4 per cent ; with an extrasystole originating in the middle third of the cycle the corresponding figures for the pause following it were 54 1 and 25 2 per cent respectively, and with extrasystoles occurring in the last third of the cycle the post-extrasystolic interval was shorter than the normal cycle length in only 8 5 per cent and longer in 80 per cent. Contrary to the conditions present in the frog's heart, in [illegible]

long refractory period of the sinus an extrasystole placed as early as the condition of the

sinus would permit was invariably followed by a longer pause than normal. As the length of the refractory period of the sinus was found to vary in different animals individual variations in the length of the post-extrasystolic intervals were common.

These conditions were found essentially to apply also in the mammalian heart (Cushny and Matthews, Hering, Lewis 1910, Sansum) and there is general agreement that, as far as the disturbance of the normal rhythm is concerned, sinus extrasystoles differ fundamentally from extrasystoles originating in any other part of the heart. The one dissenting opinion (Hirschfelder and Eyster) may, we believe, be disregarded in view of the weight of experimental evidence supporting this statement This peculiarity of sinus extrasystoles consists in the fact that the post-extrasystolic interval equals, or is only a little longer or shorter than, that between two normal periods, but is never compensatory. The explanation is that, with an extrasystole originating at the site of impulse formation of the dominant rhythm, the next impulse has to be formed anew from the moment of the extrasystole and the time required is, on the whole, equal to that between two spontaneous impulses. For this reason the view has been put forward that it would be possible to deduce from these time relations the site of normal impulse formation (Hering) It has also become clear that the conditions prevailing in the case of sinus extrasystoles provide another proof, if such were needed, for Engelmann's explanation of the compensatory pause after ventricular extrasystoles namely, that the latter is not due to any change in excitability of the heart, but simply a period of waiting for the next impulse originating in a different part of the heart; whereas a post-extrasystolic interval equalling the normal cycle length indicates impulse formation at the same site in which the extrasystole originated This law is not confined to the sinus, but holds good for any part of the heart which contains a centre of spontaneous impulse formation, for instance, the isolated perfused ventricle of the mammalian heart (Woodworth), the auricle in certain fishes (Skramlik), or ventricular extrasystoles in complete A-V block

Occasionally sinus extrasystoles may be blocked (Engelmann 1894, Skramlik; Emery and Loomis, Fig 3A)

The Electrocardiogram

In the electrocardiogram origin of an extrasystole in or near the normal pacemaker is characterized by a premature complex resembling the normal complexes in every respect and in all leads In particular the P waves have the same shape as those of the normal beats (Lewis, 1910), and the post-extrasystolic interval equals that between two normal beats or is slightly longer or shorter, but never compensatory The shortening of the post-extrasystolic interval after sinus extrasystoles is considered to be due to lengthening of the time of conduction of the extrasystole from the sino-auricular node to the auricles, conditions of sino-auricular conduction being similar to those of the A-V conduction of auricular extrasystoles (*see* p. 53) (Wenckebach and Winterberg) Since the activity of the sinus is not noticeable in records, this explanation is only an inference, though generally accepted. Another explanation was put forward by Lewis (1912), namely, that the shortening was due to " stimulation of physiological impulse formation at the point at which they arise, so that the succeeding physiological impulse is formed more rapidly than usual ", but Lewis himself stressed the rarity of this phenomenon and in the authors' opinion differences in the rate of conduction is by far the more likely explanation Slight lengthening of the post-extrasystolic interval after a sinus extrasystole may be due to variations in rate of the sinus rhythm and also to some inhibition of impulse formation in the S-A node caused by the extrasystole The arrhythmia produced by sinus extrasystoles will, as a rule, be less marked in the auricles than in the sinus, and in some cases less marked in the ventricles than in the auricles (*see also* p 48)

The above electrocardiographic criteria are the strictest that could be laid down for this

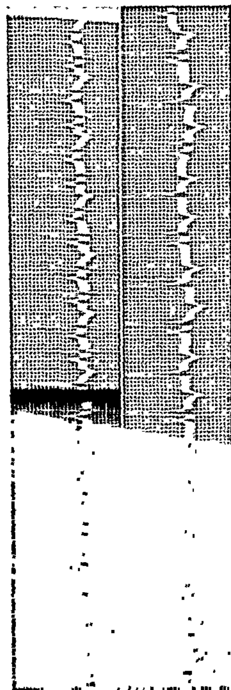


FIG 60—FIG. dog Top tracing Before and after the appearance of sinus extrasystoles elicited by the injection abaine into the head of the sinus node Bottom tracing. Sinus extrasystoles precipitated by the injection of ouabaine into the tail of the sinus node. For further explanation, see text

diagnosis to be made. Regarding clinical instances, as far as we are aware only two cases reported in the literature satisfy these conditions (Geiger and Goerner; Langendorf and Mintz, discussed below). It seems doubtful, however, whether these criteria are not too narrow It is true that absolute identity in appearance in the electrocardiogram of premature and normal complexes strongly suggests an origin of the extrasystole in or very near the sino-auricular node, but the reverse cannot be said to hold good Altered and even inverted P waves may be found in one or the other lead with premature beats which unquestionably arise in the sino-auricular node (Rothberger and Scherf, Scherf, 1945). Fig 60 provides additional experimental evidence The records were obtained from dogs, with the heart *in situ* The upper tracing was recorded during an experiment in which a fresh solution of ouabaine was injected into the area of the head of the sinus node Before the injection the cycle length measured 0 31 second Within six minutes from the injection bigeminal rhythm occurred, the extrasystoles originating at the site of injection and having a coupling of 0·25 second and the post-extrasystolic intervals measuring 0·34 second While the P waves of both beats of the bigemini have identical shapes, they differ from those present before the injection The T waves of those ventricular beats which are preceded by a short diastolic interval are deeply inverted while the QRS complexes remained unchanged. In the experiment from which the bottom tracing was obtained, ouabaine was injected into the region of the tail of the sinus node Coupled beats resulted, the P waves of the sinus beats being upright, tall and peaked, whereas those of the extrasystoles were triphasic and so shallow as to be almost isoelectric. The coupling of the extrasystoles measured 0·36, the post-extrasystolic intervals 0 52 second, the normal cycle length was 0 48 second, as shown by two successive sinus beats at the end of the tracing In both instances reproduced in Fig 60, the post-extrasystolic intervals were therefore slightly longer than the normal cycle length

These investigations demonstrate that beats originating in the sinus node may give rise to P waves of a shape different from those of the dominant sinus rhythm, either owing to disturbances of intra-auricular conduction or to a different site of origin within the sino-auricular node Moreover, the post-extrasystolic interval may be slightly longer than the normal cycle length Applying this to arrhythmias recorded in man, it must be conceded that some degree of differences in shape of the P waves of the premature beats do not necessarily exclude their sino-auricular origin, for instance the case of Lewis, 1912, section 2 and Fig 10.

In cases of bigeminal action due to beats of sinus origin the difficulties regarding the diagnosis of sinus extrasystoles are further increased by the fact that various disturbances in impulse formation in the sino-auricular node other than sinus extrasystoles, and sino-auricular disturbances of conduction, can produce identical arrhythmias Regarding the latter, 3 : 2 sino-auricular block with or without Wenckebach's periods, may be mentioned. The various mechanisms are clearly illustrated diagrammatically in a paper by Clerc, Lévy and Calo.

These considerations afford an understanding why the diagnosis of sinus extrasystoles in man can unreservedly be accepted in only very few of the reported instances, now to be discussed

Clinical Observations

As already mentioned, only two cases reported in the literature satisfy the strictest conditions as described above Geiger and Goerner's patient, a man of sixty-four with carcinoma of the oesophagus, exhibited coupled beats, occasionally interrupted by a series of three regular beats of constant rate The complexes of the premature beats were identical in all leads, including amplified semi-direct chest leads, with those of the dominant rhythm. The cycle length of the normal beats was 0·96 second, the coupling of the premature beats

0 68 and the post-extrasystolic intervals 0 96, that is equalled the normal cycle length It was possible in this case to exclude other kinds of sinus arrhythmia, for instance simple sinus arrhythmia (phasic respiratory as well as non-phasic independent of respiration), sino-auricular block and auricular extrasystoles The other instance is Case 1 of Langendorf and Mintz In records obtained from a sixty-year-old man all leads except lead I showed coupled beats, P-P intervals of 0 98 second alternating with those of 0·80 During the undisturbed rhythm recorded in lead I, the P-P intervals measured 0 98 second, that is were of the same length as the long intervals during bigeminal action These time relations make it possible to exclude other arrhythmias of sinus origin with a fair degree of probability and to consider the arrhythmia to be due to sinus extrasystoles with post-extrasystolic intervals equalling the normal cycle length.

Another possible instance was reported by Schlachman. In a man of fifty-six with pernicious anaemia he recorded a bigeminal rhythm in which the two beats had identical shape The P-P intervals alternated between 0 68 and 0 96 second The bigemini persisted in maximum expiration and during carotid sinus pressure, but was absent in maximum inspiration and abolished by amyl nitrite When the number of R B.C had risen from 1,580,000 to 3,820,000, only simple sinus arrhythmia was recorded Schlachman's interpretation of the arrhythmia as sino-auricular extrasystoles cannot be considered proved, as two successive normal beats were never recorded during the arrhythmia, and no evidence is given that the first and second beat of the bigemini had identical shape in all leads Moreover, the intervals do not allow to exclude sino-auricular 5 3 block and the arguments put forward in favour of sino-auricular extrasystoles as against S-A block are not wholly convincing However, this observation can be considered as a possible, though not proved instance of this rare arrhythmia

As far as it is possible to make a diagnosis from one lead Fig 61 may provide an example of a sinus extrasystole The tracing, obtained from a patient with hypertension, shows a regular sinus rhythm with a cycle length of 1·36 second Occasionally premature beats occurred, resembling in every respect those of the dominant rhythm Their coupling always measured 1 0 second and the post-extrasystolic interval 1·32 seconds, that is was slightly shorter than a normal period Such extrasystoles were recorded three times in lead I, whilst they were absent in the other leads

Regarding the case of Lewis (1912), *see above*

In Laslett's case the records are quite inadequate for an accurate diagnosis of the arrhythmia to be possible A

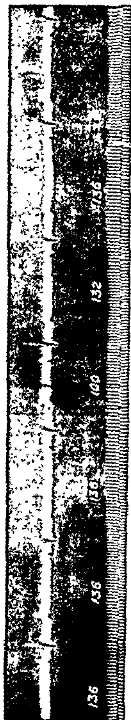


Fig 61 —Lead I The fourth beat is most probably a sinus extrasystole The post-extrasystolic interval is shorter than the cycle length of the normal rhythm

case reported by Wenckebach and Winterberg is better explained by assuming the presence of auricular extrasystoles, some of them conducted and some blocked. What is regarded by those authors as the "normal period" seems to include a blocked auricular extrasystole, shown in the phlebogram by a notch in the descending limb of the *v* waves Schill reported a case of numerous sinus extrasystoles with disturbances of conduction of several kinds, but, as far as the short reproduced records allow of any analysis, the arrhythmia was due to auricular extrasystoles, some of them blocked. His interpretation of a case of sinus arrhythmia, reported by Fogelson, as being an instance of numerous sinus extrasystoles is unacceptable; as far as the published data make a more detailed diagnosis possible, auricular extrasystoles and periods of paroxysmal auricular tachycardia seem a far more likely explanation

SUMMARY

The fundamental difference between extrasystoles originating in the sino-auricular node and those arising in any other part of the heart consists in the fact that the post-extrasystolic interval of the former equals, or is only a little longer or shorter than that between two normal periods, but is never compensatory. The reason for this is discussed, and the relevant experimental work is reviewed In the electrocardiogram origin of an extrasystole in or very close to the normal pacemaker is characterized by a premature complex resembling the normal complexes in every respect and in all leads, the length of the post-extrasystolic interval being as stated above. It is pointed out that the above criteria require some extension in certain circumstances In view of the results of experimental work, neither a different shape of the P waves of the premature beats, provided their P-R intervals do not exceed those of the normal ones, nor a post-extrasystolic interval slightly exceeding the normal cycle length exclude sinus extrasystoles, but in such instances an auricular origin of the premature beats cannot be ruled out The reported cases of sinus extrasystoles in man are critically reviewed and only very few of them can be accepted as such without reserve. While the presence of sinus extrasystoles in man is established their occurrence is extremely rare.

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INTERPOLATED EXTRASYSTOLES

Interpolated extrasystoles are those which are interposed between two beats of the dominant rhythm occurring in their usual sequence.

In the discussion on ventricular extrasystoles it was pointed out that the normal impulse following the extrasystole usually fails to yield a ventricular contraction because it occurs at a time when the ventricles still are in the refractory period of the extrasystole If, however, the heart rate is slow and the extrasystole occurs early in diastole, the refractory period of the conducting system and of the ventricles may already have terminated by the time the first post-extrasystolic sino-auricular impulse arrives, and a ventricular contraction will follow In these circumstances a ventricular extrasystole will occur between two successive sino-auricular beats

Disturbance of Rhythm

Fig 62 illustrates diagrammatically the disturbance of rhythm caused by an interpolated extrasystole The cycle length of the auricular rhythm is assumed to be constantly eighty-hundredths of a second Following the second normal beat a ventricular extrasystole is assumed to occur with a coupling of 0·28 second The first post-extrasystolic beat (Beat No 3) is shown to be conducted to the ventricles with a slightly lengthened atrio-ventricular conduction time [illegible] tion) is shortened by that amount

Interpolated extrasystoles are the only variety of "extra" systoles in the sense of being additional, supernumerary beats

It will be shown below that, apart from the prevailing sinus rate and the degree of prematurity of the extrasystole, other factors are of importance in determining whether a ventricular extrasystole will be interpolated or followed by a compensatory pause

These remarks refer to interpolated ventricular extrasystoles in cases of sinus rhythm It is obvious that interpolated extrasystoles can occur only if the formation of impulses in the centre of the dominant rhythm is unaffected by the extrasystole Therefore, interpolated extrasystoles usually originate in a chamber of the heart other than that containing the centre of impulse formation of the dominant rhythm, that is, in the mammalian heart, in the ventricle, in the heart of certain fishes and reptiles (where the centre of normal impulse formation is situated in the separate sinus), in the auricle or ventricle In the mammalian heart, in exceptional circumstances (*see* below) interpolated extrasystoles may originate in

the same chamber in which the centre of impulse formation of the prevailing rhythm is located, namely, interpolated auricular extrasystoles, or interpolated ventricular extrasystoles in complete A-V block.

Regarding observations in a case of interpolated A-V extrasystoles (Bix), *see* section on "Atrio-ventricular Extrasystoles", p 73.

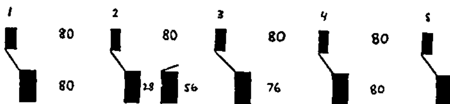


Fig 62 —Diagram illustrating the disturbance of rhythm caused by an interpolated extrasystole The figures indicate intervals in hundredths of a second (except the top row which indicates consecutive numbers of S-A beats) For explanation, see text

Interpolated ventricular extrasystoles during sinus rhythm

This is the only variety which, though by no means common, occurs with any frequency in man and is of any clinical significance.

Interpolated ventricular extrasystoles may have first been observed by Galen and by Senac (*see* historical remarks) and possibly by Marey (Busquet; Dresbach and Munford), though this is denied by others (Myers and White) They were certainly often seen experimentally and correctly interpreted [Lovén, Engelmann, Kaiser, Woodworth, Rihl 1904, Trendelenburg (frog), Bethe (caput medusae)] In man they were first described by Wenckebach in 1899 on the grounds of an analysis of the radial pulse only (*see* also Wenckebach 1903, 1906) His interpretation was subsequently confirmed by means of venous pulse tracings by Pan (1903 and 1904), and further descriptions soon followed (Volhard; Gerhardt, Laslett; Staehelin and Nicolai, Dresbach and Munford, Myers and White)

Amongst 5,000 electrocardiograms obtained in the Massachusetts General Hospital from 2,392 patients in the course of six years, ventricular extrasystoles occurred in 284 tracings from 200 patients Of these, twenty-four tracings obtained from fourteen patients showed interpolated extrasystoles, that is 7 per cent. of the patients exhibiting ventricular extrasystoles (Myers and White)

Fig 63, reproducing a record from a fifty-nine-year-old man with syphilitic aortic incompetence, shows signs of left ventricular hypertrophy and myocardial damage (slurred QRS complexes, deep notched Q waves in lead 3 and abnormal final deflections) Interpolated ventricular extrasystoles occurred in every second diastole although the rate of the sinus rhythm was as high as eighty Only in lead CR-4 was one extrasystole followed by a compensatory pause

The atrio-ventricular conduction of the post-extrasystolic beat after interpolated extrasystoles often is delayed, particularly with higher rates (Pan, Mackenzie, *see* also Figs 63 and 64). Lengthening of the P-R intervals of these beats was found in about 50 per cent. of the cases and intervals as long as 0·78 second have been reported. The subsequent diastole is correspondingly shortened. In some cases the P-R interval of the second post-extrasystolic beat also may be prolonged (Katz *et al*) Moreover, aberrant intraventricular conduction of the post-extrasystolic beat is not uncommon. in some instances only changes in the T wave occur (*see* Fig. 65a), more frequently the QRS complex shows

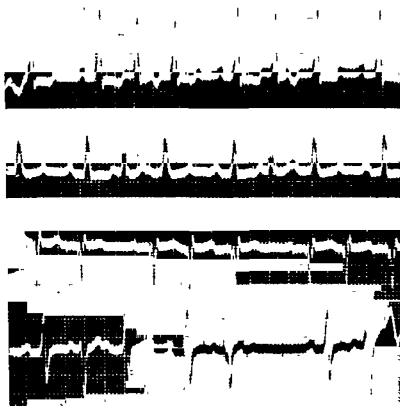


FIG 63—The three standard leads and lead CR-4 Interpolated ventricular extrasystoles in every second diastole, except for the second extrasystole in lead CR-4 which is not interpolated

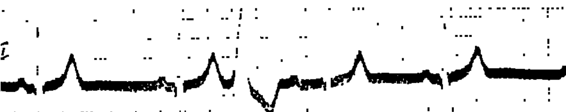


FIG 64—Changes in the first post-extrasystolic beat after an interpolated extrasystole Lead 2 Lengthening of the P-R interval to 0 28 sec as compared with 0 16 sec of the sinus beats

marked anomalies (*see* Fig 65b). Occasionally several post-extrasystolic beats may be affected (*see* Fig. 66). These changes in the features of the post-extrasystolic beat(s) are due to disturbances of conduction resulting from an incomplete recovery of the conducting system, after the greater demands made upon it by the two preceding beats following one another at a short interval This is easily understood in the case of extrasystoles originating above the bifurcation and being conducted to the ventricles via the normal paths. But even in the far commoner case of an interpolated extrasystole originating below the bifurcation it has to be assumed that it is conducted over a certain distance through specialized



FIG 65 —Changes in the first post-extrasystolic beat after an interpolated extrasystole *a* affecting the T wave; *b* affecting the QRS-T complex.

fibres (*see* p 373) The distance can only be a short one, as only a short time interval separates the interpolated extrasystole from the post-extrasystolic beat. It is unlikely that such retrograde conduction should go further than the A-V node.

Ashman, by way of explaining the lengthening of the P-R interval of the post-extrasystolic beat without any alteration of its ventricular complex, pointed out that if the extrasystole is conducted in a retrograde direction to the A-V node, the delay in the conduction of the post-extrasystolic beat takes place in the A-V node with the result that, by the time the impulse reaches the bundle branches and their ramifications, their recovery is already complete. A different explanation put forward by Straub in 1918 that the lengthening of the P-R interval of the post-extrasystolic beat is due to a greater latency of the ventricles is now generally discarded

The above considerations tend to show that very small changes in the time sequence of extrasystole and post-extrasystolic impulse will determine whether an extrasystole is interpolated or followed by a compensatory pause In addition to the rate of the prevailing sinus rhythm and the degree of prematurity of the extrasystole, the rate of recovery of conductivity and excitability also will be of importance, that is the length of the refractory period, for the duration of which vagal tone is (amongst others) a decisive factor. This affords an understanding for the observation that, of ventricular extrasystoles occurring in the same phase of diastole, some may be interpolated whereas others are not; sometimes in the same tracing, without any change in the sinus rate, extrasystoles may paradoxically be followed by a compensatory pause though they occurred earlier in diastole than interpolated ones (Wenckebach and Winterberg, p 179)

Two interpolated extrasystoles within one diastole have been described (Pan, 1904), but so far as we are aware this phenomenon has not been recorded electrocardiographically. It is not uncommon, however, that two (*see* Fig 67) and rarely even three extrasystoles may replace one normal beat so that one or two respectively of these extrasystoles could be considered interpolated

Clinical Significance

Isolated, single interpolated ventricular extrasystoles have the same clinical significance and produce the same symptoms as any other type of extrasystole If, however, an interpolated extrasystole occurs after every normal beat over a certain period, the ensuing sudden doubling of the ventricular rate may easily be misinterpreted as paroxysmal tachycardia (Gerhardt) or auricular flutter

Fig 68 shows two instances of this kind of arrhythmia In the top tracing (Fig, 68a) the ventricular rate rose during the occurrence of the interpolated extrasystoles from about 72 to about 144 and the post-extrasystolic beats showed marked aberration of the QRS complexes; in the bottom tracing (Fig 68b) the interpolated extrasystoles caused a rise in the ventricular rate from 59 to 118 and the A-V conduction time of the post-extrasystolic beats was lengthened Interpolated extrasystoles have therefore to be included amongst the conditions which may give rise to a sudden doubling of the ventricular rate, the commonest cause of this seems to be auricular flutter with sudden change in the degree of block, or paroxysmal tachycardia may be responsible.

Blanc reported an unusual observation in a man of fifty-seven suffering from syphilis and attacks of angina pectoris, in whom interpolated extrasystoles were recorded after every second beat only during the anginal attacks

Pulse Changes

In the case of interpolated extrasystoles characteristic pulse changes may occur which can be of diagnostic help

Owing to the marked prematurity of the extrasystole its stroke volume often is so small that it does not produce a palpable pulse at the wrist The pulse produced by the post-extrasystolic beat usually is smaller than the normal one (owing to a partial emptying of the ventricles by the extrasystole and interference by the extrasystole with diastolic filling) and, as a result of delay in conduction of the post-extrasystolic beat and the prolonged pre-sphygmic time associated with the smaller stroke volume, the pulse wave of this beat reaches the wrist with a certain delay The subsequent pulse, on the other hand, has a larger volume, since a longer time interval was available for the diastolic filling between the post-extrasystolic and the subsequent beat as compared with the interval between the extrasystole and the post-extrasystolic beat, moreover, as the interval following the post-extrasystolic beat is somewhat shortened, the second pulse following an interpolated extrasystole will be felt after a slightly shorter interval The changes produced by an interpolated extrasystole will therefore consist of the sudden occurrence of a



FIG 66 —Changes in the first three post-extrasystolic beats after an interpolated extrasystole Time base 0 05 second

smaller pulse occurring with a slight delay, followed by a larger pulse occurring after a slightly shortened diastole This sequence can be of some diagnostic significance (Lian and Jonas). Owing to the features described, the pulse produced by a series of interpolated extrasystoles may give the impression of being a *pulsus alternans*; it has been termed *pulsus pseudoalternans* by Myers and White.

Interpolated Auricular Extrasystoles

It has been pointed out above that interpolated extrasystoles are far more likely to originate in a chamber of the heart other than that containing the pacemaker of the dominant rhythm Thus in fishes and reptiles, in which the normal pacemaker is situated in the separate sinus, interpolated auricular extrasystoles are not uncommon (Lovén, Skramlik, Trendelenburg, 1909), and they are occasionally seen also in frogs in spite of the slow rate of retrograde conduction in amphibia In the mammalian heart, on the other hand, in which auricular extrasystoles are either followed by a compensatory pause or, more commonly, are conducted to the sino-auricular node where they discharge the immature normal impulse, interpolated auricular extrasystoles can occur only in exceptional circumstances.

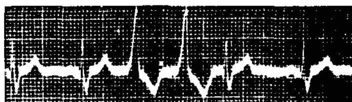


Fig 67 —Two ventricular extrasystoles replacing one sinus beat

Thus Kisch described interpolated auricular extrasystoles in the dying rabbit heart and their occurrence was explained by the assumption that the damaged tissue failed to conduct in the usual way the extrasystole which thus failed to reach the sinus node Direct leads from the auricular muscle proved the presence of partial contractions

Interpolated auricular extrasystoles in the dog were found by Drury and Brow in six out of ten animals Auricular extrasystoles were produced by means of induction shocks, the electrodes being at a distance of 0·5 to 1 cm from the sinus node In some experiments the rate of stimulation was but slightly higher than the spontaneous rate, with the result that some extrasystoles occurred very early in diastole and reached the sinus node very shortly after the discharge of its preceding impulse. As the refractory period of the sinus node is considerably (about 30 per cent) longer than that of the auricular muscle some extrasystoles reached the sinus node while still in the refractory stage This was found to be the case if the extrasystolic impulse arrived at the sinus node 0 22 second after the discharge of the last preceding impulse It is obvious that the long duration of the refractory period of the sinus node is a pre-requisite for auricular extrasystoles to be interpolated According to Drury and Brow, only if this exceeds the normal sino-auricular conduction time, plus the refractory period of the auricle plus the time required for the retrograde conduction of the extrasystole to the sinus node, will an auricular extrasystole be interpolated

Interpolated auricular extrasystoles were also seen experimentally by Eccles and Hoff

No case of interpolated auricular extrasystoles in man has yet been published in which the diagnosis could be accepted unreservedly by us In a case published by Rihl (1926), in which this diagnosis was put forward for the first time, another interpretation was conceded by the author himself, since the auricular periods, during which the possibly

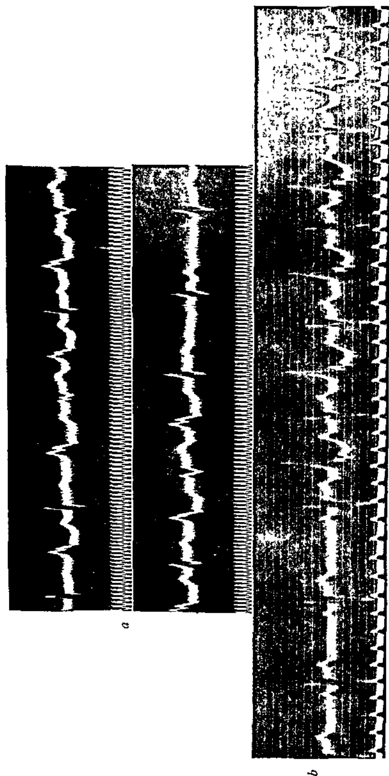


Fig 68.—Two instances of interpolated ventricular extrasystoles, occurring in bigeminal form, resulting in a sudden doubling of the ventricular rate *a* The two strips are continuous Time base 0 04 sec ; *b* Time base 0 2 sec

interpolated auricular extrasystoles occurred, were consistently shorter than the normal periods, moreover, the P waves of the beats following the extrasystoles had abnormal shapes. Cases published by others actually represent multiple auricular extrasystoles (Calabresi, Reid). In the tracings of Burghard and Wunnerlich artefacts simulated the arrhythmia. Weinberg and Katz's case is not convincing because it can be explained by the presence of auricular extrasystoles in a case with bizarre but not unusual T waves in the chest leads. A case described in detail by Wenckebach and Winterberg (p 193) shows how easily successive auricular extrasystoles may be mistaken for interpolated auricular extrasystoles Normal P waves of the beats preceding and following the auricular extrasystole have to be postulated, in addition to the appropriate time relations, for a diagnosis of interpolation to be made In this respect the most convincing case so far is that published by Gonczy and Gyorgyi The tracing, obtained from a patient with rheumatic mitral valvular disease, showed the occurrence of a premature auricular systole followed by a beat with a P wave of the same shape as that of the other sino-auricular beats and occurring at the normal time Longer tracings, however, showing the post-extrasystolic rhythm, would be necessary to establish the diagnosis with certainty. It may be mentioned in passing that polygraph tracings are inadequate for the diagnosis of this arrhythmia, as they give no

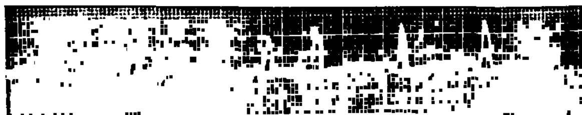


FIG 69—Lead I The third sinus beat is followed by two auricular extrasystoles though the possibility of an interpolated auricular extrasystole cannot be definitely excluded

indication about the site of origin within the auricle of the impulse of the post-extrasystolic beat, such information, however, is indispensable in order to exclude an ectopic origin of the post-extrasystolic beat and thus to exclude multiple auricular extrasystoles.

Fig 69 illustrates the difficulties in interpretation even from the electrocardiogram. The first three beats are sinus beats showing the features of left bundle branch block, with cycle lengths of 0 85 and 0·87 second respectively. The third sinus beat is followed by an auricular extrasystole with slight aberration of intra-ver
difficulty arises in respect of the next beat (the fifth of
beat may be interpreted as being that of a normal si
auricular extrasystole If the former interpretation is accepted, the preceding auricular extrasystole would be an interpolated one The identity in shape of the P wave of this beat with that of the P waves of the sinus beats would be in favour of this view. On the other hand, the interval between the P waves of the beats preceding and succeeding the auricular extrasystole (that is, the interval between the P waves of the third and fifth beats) measures 0·91 second and is thus distinctly longer than the cycle length of the sinus rhythm. The most probable conclusion therefore is that the fifth beat is also an auricular extrasystole, and that the third sinus beat is followed by two auricular extrasystoles in succession; but an interpolated auricular extrasystole cannot be excluded with certainty in this instance

Therefore, while interpolated auricular extrasystoles have experimentally been demonstrated in the mammalian heart, their occurrence in man cannot yet be considered as established

Interpolated Ventricular Extrasystoles in Idio-Ventricular Rhythm (complete Atrio-Ventricular Block)

In man, ventricular extrasystoles occurring in complete heart block are nearly always followed by an interval equal to that between two idio-ventricular beats (*see* p. 96). The obvious explanation is that the extrasystoles, originating in the same chamber as the impulses of the dominant ventricular rhythm, are conducted to the centre of impulse formation of the idio-ventricular beats where they discharge the immature impulse For the same reason interpolation will occur only in exceptional circumstances in such cases

Interpolated ventricular extrasystoles in the automatically beating ventricle were seen by Woodworth, Hofmann and Holzinger, and Koch While it is possible that this was due to partial contractions of the ventricle or its hypodynamic state, it is more likely that the underlying mechanism was a protective "block" (discussed on p 168) of the idio-ventricular centre

In man a case of interpolated ventricular extrasystoles in complete heart block and auricular fibrillation was described by Weiser in a digitalized patient. The ventricular periods measured 1 5 second, the period which contained the extrasystole, 1 55 second. The slight lengthening of this period was attributed to an inhibitory effect of the extrasystole on the formation of the next stimulus, this explanation, however, seems unlikely



Fig 70 —Lead 2 Complete heart block with ventricular extrasystole which did not disturb automatic ventricular rhythm, thus is "protectively blocked" The extrasystole is interpolated From Scherf and Boyd *Clinical Electrocardiography* Wm Heinemann, London

as the extrasystole, being interpolated, could not have reached the centre In some of the cases of interpolated ventricular extrasystoles with auricular fibrillation and A-V block (Frey, Fahrenkamp, Wolferth), a similar lengthening (by 0 06–0 07 second) of the period containing the extrasystole was found (Wolferth)

A good example of interpolated ventricular extrasystoles during sinus rhythm and complete heart block was described by Scherf and Boyd (*see* Fig 70).

SUMMARY

Interpolated extrasystoles are defined as those which are interposed between two beats of the dominant rhythm occurring in their usual sequence The disturbance of rhythm caused by this variety is described and diagrammatically illustrated. The only variety which occurs with any frequency and is of any clinical significance is the occurrence of interpolated ventricular extrasystoles during sinus rhythm This variety is described in some detail and illustrated by examples The first post-extrasystolic beat is often conducted with some delay which has to be located in the A-V node The clinical significance of interpolated extrasystoles is on the whole the same as that of non-interpolated ones; only if one interpolated extrasystole follows each beat of the dominant rhythm over longer periods may a sudden doubling of the ventricular rate ensue. The pulse changes produced by an interpolated extrasystole are described and their mechanism analysed It is pointed out that, as a rule,

interpolated extrasystoles originate in a chamber of the heart other than that containing the pacemaker of the dominant rhythm. In the mammalian heart, therefore, interpolated auricular extrasystoles can occur only in exceptional circumstances, some of which reported in the literature are briefly discussed. Instances of this arrhythmia reported to have been observed in man are critically reviewed, and it is pointed out that no such case can be accepted unreservedly and that the occurrence of this arrhythmia in man cannot be considered as established

A personal observation is described in which this possibility has to be conceded though the interpretation favoured by us is that the record in question demonstrates two auricular extrasystoles following in succession Interpolated ventricular extrasystoles in complete A-V block occur only in exceptional circumstances; the few reported instances, experimental and clinical, are briefly reviewed.

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EXTRASYSTOLES ORIGINATING IN THE STEM OF THE BUNDLE OF HIS

Extrasystoles originating in the stem of the bundle of His—stem extrasystoles for short—are, in one sense, ventricular ones Owing to their arising above the bifurcation of the bundle, however, they differ from the common varieties of ventricular premature beats in this one important respect that they spread through the ventricles along the same paths as supraventricular beats. While they have this in common with A-V nodal extrasystoles, they differ from these, and resemble the great majority of the common ventricular ones, in that the auricles continue to be activated by the S-A node This is due to the blocking of the retrograde spread of the extrasystoles to the auricles which takes place in the A-V node It follows that stem extrasystoles cannot be differentiated from A-V nodal ones with blocked retrograde conduction to the auricles

The diagnosis of stem extrasystoles is based on the following electrocardiographic features a premature beat occurred, the ventricular complex of which has in all leads the same shape as those of the supraventricular beats, there is undisturbed sequence of the P waves, the P wave related to the premature beat has in all leads the same shape as those of the supraventricular beats, the post-extrasystolic intervals are compensatory

The P wave related in time to the premature beat—that is the P wave of the normal sinus impulse with blocked conduction to the ventricles—may precede its ventricular complex with a shortened P-R interval (Lewis, Fig 1) or (more frequently) follow it In the latter case it is visible between the QRS and T wave of the premature beat (Lewis, Fig 2, Lewis and Allen, Holzmann)

Extrasystoles with this site of origin are very rare In many textbooks they are not even mentioned, and the number of published cases is very small One case each was reported by Lewis, and by Lewis and Allen, in both such origin was considered probable and we would associate ourselves with this interpretation In the first of these instances the diagnosis seems correct particularly in view of the record reproduced in the author's Fig. 12. In the latter the necessity of assuming aberration of intra-ventricular spread introduces a

difficulty without however disproving the interpretation offered. Wenckebach and Winterberg reproduce a record interpreted as A-V extrasystoles with blocked conduction to the auricles, which, as stated above in this section, could equally well be considered as showing stem extrasystoles. Two instances fulfilling the above diagnostic criteria and interpreted as stem extrasystoles have been published by Holzmann

Fig 71 provides an example of a probable instance of a stem extrasystole. The record showed the features of left bundle branch block with lengthening of the P-R intervals. Periodically premature beats were recorded which had in all leads the same shape as the sinus beats. The post-extrasystolic intervals were compensatory. P waves of the sinus impulse with blocked conduction to the ventricles were not visible in the reproduced or in any of the other leads, but they invariably occurred at a time when they were buried in the QRS complex of the extrasystole.

To our knowledge oesophageal leads have not yet been recorded in this type of extrasystoles This would be essential to clarify the question of retrograde conduction of such beats to the auricles

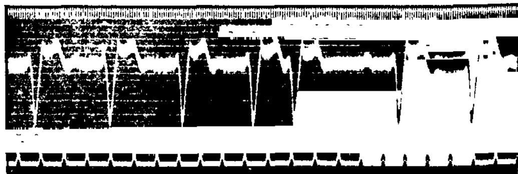


Fig 71 —Lead 3. Left bundle branch block with lengthening of the P-R

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EXTRASYSTOLES IN COMPLETE A-V BLOCK

Introductory Remarks

In addition to their clinical importance extrasystoles occurring in complete A-V block present features of special physiological interest, since they illustrate some aspects of the mechanism underlying normal impulse formation and conduction

In the great majority of cases of extrasystoles observed in man they originate in a part of the heart which is anatomically or functionally separate from that containing the pacemaker of the dominant rhythm But, if extrasystoles occur in complete A-V block, in which

the ventricles are stimulated by impulses originating in a ventricular centre, the extrasystoles and the automatic beats arise in the same part of the heart, and a disturbance of rhythm results which differs from that observed in the more common kinds of ventricular extrasystolic arrhythmias

Experimental Observations

This phenomenon has been extensively studied experimentally While a brief reference can be found in a paper by Cushny and Matthews in 1897, the first detailed investigation of the effect of extrasystoles upon the rhythm of the automatically beating mammalian ventricle was carried out by Woodworth in 1902 on the perfused apex of the dog's ventricle. He established the fact that the interval following an extra-contraction was not compensatory, but approximated the interval between two spontaneous beats, being as a rule slightly shorter than the normal cycle (94 1 per cent.) and tending to be shorter the earlier in diastole the extra-contraction occurred. In some of his experiments (for instance his Fig 5) the degree of shortening is so great that doubts seem justified whether his interpretation of some of his tracings is acceptable; as only mechanical records were obtained the possibility of two or more extrasystoles following the stimulus cannot be excluded

Hering (1905a) pointed out that the length of the post-extrasystolic interval in the isolated mammalian ventricle usually equalled the normal cycle length, and that the same conditions prevailed as in extrasystoles elicited from, or very near, the pacemaker of the dominant rhythm, that is the *sinus venosus* or great veins of the frog's heart or the orifices of the great veins of the mammalian heart In all such cases the extrasystole, arising in, or very close to, the centre of origin of the dominant rhythm, there destroys the immature impulse of the next automatic beat, approximately the same time is required for the next impulse to become effective as elapses between two automatic beats so that the post-extrasystolic interval equals the normal cycle length Hering therefore recommended using these time relations in order to test by means of extra-stimuli whether, in a given experiment, the centre of automatic impulse formation is situated in the ventricles. Hering's reasoning was that only if the post-extrasystolic interval equals, or is slightly shorter than, the normal cycle length is it certain that automatic ventricular rhythm is present Post-extrasystolic intervals slightly longer than the spontaneous periods also occur in idioventricular rhythm, but do not prove its presence, since they may be caused by ventricular extrasystoles with retrograde conduction to the auricles For a discussion of the older literature, *see* Rihl

With the advent of electrocardiography such measurements as advocated by Hering have become unnecessary for the purpose of ascertaining the presence or otherwise of idioventricular rhythm, but the underlying principle would still be of considerable general physiological interest if such time relations were confined to ventricular extrasystoles in complete A-V block, as Hering thought This, however, is not the case, since similar time relations may be present in partial A-V block

The effect upon the ventricular rhythm of ventricular extrasystoles in partial A-V block is not uniform, and Erlanger's statement (1906) that it is the same as in complete A-V block cannot be accepted as valid for most cases The post-extrasystolic intervals in partial A-V block may, as in cases of complete A-V block, equal the normal [illegible] W[illegible]
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[illegible]
coupling of the ventricular extra-contraction [illegible] the post extrasystol[illegible]
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erroneous conclusion that an automatic ventricular rhythm is present, unless the auricular contractions are also recorded Actually, in Wertheimer's experiments the ventricular

contractions were initiated by the normal pacemaker throughout, but as a result of the ventricular extrasystole a permanent shift of the ventricular rhythm occurred If, however, owing to a more persistent impairment of conduction, the subsequent auricular impulse also fails to be conducted and the length of the coupling + the post-extrasystolic interval therefore equal the length of four auricular cycles, the post-extrasystolic interval becomes compensatory and no permanent shift of the ventricular rhythm takes place, since the original ventricular rhythm is resumed with the first post-extrasystolic beat. In some, but not all cases of this kind, the post-extrasystolic interval is slightly shorter than compensatory, owing to increased speed of conduction of the post-extrasystolic beat, this being due to the longer period of recovery provided by the long post-extrasystolic interval.

To return to conditions in complete A-V block. the salient fact is that the post-extrasystolic interval in the automatically beating ventricle equals or closely approximates the normal cycle length The one dissenting report about the occurrence of true compensatory pauses in such circumstances (Rothberger and Winterberg) is explained by the high ventricular rate, and the long distance between the focus of origin of the extrasystoles and that of the automatic ventricular rhythm in their experiments, and does not invalidate the above statement Regarding the exact length of the post-extrasystolic intervals some differences were found in different species and under different experimental conditions, as briefly mentioned above. In the isolated frog's ventricle it was found to be somewhat longer than the normal cycle length, and the lengthening increased with the degree of prematurity in diastole of the extrasystole (Hofmann and Holzinger) In the automatically beating mammalian ventricle, on the other hand, the post-extrasystolic interval often equals the normal cycle length or may be a little longer or shorter, but is never compensatory (Hering, 1905a; Erlanger, Hofmann and Holzinger)

By reducing the concentration of NaCl to 0·5–0·2 per cent., or by increasing the concentration of KCl, in the Locke solution, an inhibitory action of extrasystoles upon the following beat could be produced in the automatically beating mammalian ventricle when this had not been present before; this effect was shown to be directly due to the electrolytes and not to differences in the rate of flow (Hofmann)

It can therefore be said that extrasystoles in the automatically beating ventricle produce a permanent disturbance of the ventricular rhythm, the post-extrasystolic interval being equal to, or somewhat longer or shorter than, the automatic cycle length, but never compensatory in nature or (with rare exceptions) in length. Shortening of this interval may be explained either by a stimulating effect of the extra-contraction, analogous to conditions prevailing in some cases of auricular extrasystoles (*q.v.*), or to the same mechanism which is responsible for the shortening of the post-extrasystolic interval after sinus extrasystoles (*see* pp. 79 *seq*).

In the mammalian heart and in clinical observations lengthening of the post-extrasystolic interval in such cases is far more common than shortening and has to be ascribed to an inhibitory action of the extrasystole upon the impulse formation of the following automatic beat (*see* section on "Auricular Extrasystoles", pp 47, 55). In dogs, in which complete heart block was produced by clamping the A-V bundle, the degree of the inhibitory effect upon the ventricular action of ventricular extrasystoles was shown to depend on the rate and duration of the stimulation and on the condition of the heart (Erlanger and Hirschfelder); similar conditions were demonstrated in cats with asphyxial heart block (Lewis and Oppenheimer). The clinical importance of these findings will be discussed later in this section.

Clinical Observations

Whereas in man auricular extrasystoles in complete A-V block are very rare (Brown; Deglaude and Zadé; Holzmann; Katz), ventricular extrasystoles are relatively common (Hoesslin) This is understandable in view of the fact that conditions which are known to

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be common causes of A-V block are also prone to give rise to ventricular extrasystoles, for example, coronary sclerosis or diphtheria and, amongst drugs, digitalis. It is also evident that a lesion which, by being situated in a portion of the conducting system, causes block is also likely to cause extrasystoles since they originate in the same kind of tissue. They may occur so frequently as to produce bigeminal rhythm.

Fig. 72 was obtained from a sixty-nine-year-old woman with complete A-V block and Stokes-Adams attacks The Wassermann reaction was positive The patient was given ephedrine grain ½ thrice daily. The record shows complete A-V dissociation, the P waves being bifid. The cycle length of the automatic ventricular rhythm was constantly 1·50 seconds, the post-extrasystolic interval measured 1·53 seconds.

Fig 73 was obtained from a fifty-two-year-old patient with coronary sclerosis, admitted with pulmonary oedema He was given digitalis and complete A-V block occurred in the course of treatment. The interval between the first two automatic beats was 1·16 seconds. After the second automatic beat two extrasystoles occurred which were followed by an interval of 1·33 seconds. The interval following the next extrasystole measured 1·28 seconds This record illustrates extrasystoles in complete A-V block followed by post-extrasystolic intervals moderately longer than the normal cycle length. This lengthening was more pronounced in the interval following two successive extrasystoles than in that following a single one, which is in accordance with the experimental observations quoted above.

In man a pronounced shortening of the post-extrasystolic interval in complete block is rare, but has occasionally been found (Naish, Frey)

In patients with A-V block the automatic beats (*see* Gilchrist and Cohn) and also the extrasystoles may show varying forms in the electrocardiogram (Scherf, Scherf and Schott) In a certain proportion of such cases an automatic beat following an extrasystole shows the same shape as the preceding automatic beat and it is this observation which made it possible to decide that the varying form is due to a change in the site of impulse formation and not to disturbances of conduction of the extrasystolic impulse. This conception, which also has a bearing

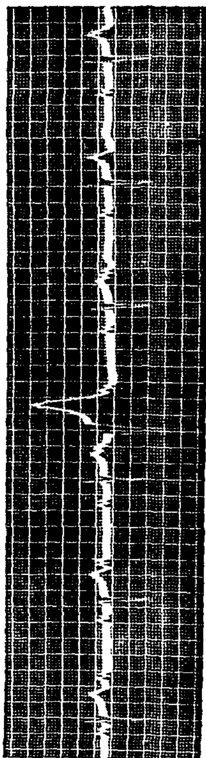


FIG 72.—*Lead CR-2.* Ventricular extrasystole in complete A-V block

on the differentiation between automatic and extrasystolic impulse formation (*see* p. 492), is in accordance with experimental findings on the activity of several centres of impulse formation in the ventricles after severing both branches of the bundle of His (Wilson and Herrmann). Clinically, the combination of complete or partial A-V block with bundle branch block is by no means uncommon. In such cases both bundle branches are affected, the A-V node and main bundle being found normal histologically. This localization of degenerative lesions is due to the fact that the A-V node and bundle derive their

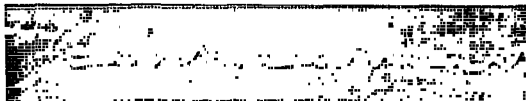


FIG 73.—Lead 2 Ventricular extrasystoles in complete A-V block with lengthening of the post-extrasystolic periods

blood supply from a source different from that of the blood supply of the bundle branches (Yater, Cornell and Claytor) The presence of active foci in both main branches renders the prognosis more grave

Fig. 74, recorded in a seventy-five-year-old patient, provides an example. The tracing shows complete A-V block The first two ventricular complexes were directed upwards, the initial portions being widened to 0·11 second and the R-R interval being 1·16 seconds. The second beat was followed after an interval of 0·68 second by an extrasystole the main deflection of which was directed downwards, and the two subsequent automatic beats had the same shape as the extrasystoles; the cycle length had increased to 1·28 seconds and the duration of the initial ventricular deflections to 0·16 second

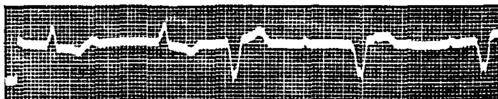


FIG 74.—Lead 2 Ventricular extrasystole in complete A-V block, followed by automatic ventricular beats of the same shape as the extrasystole, indicating change in the site of origin of the idioventricular beats

As a rule extrasystoles in complete A-V block tend to increase the low ventricular rate and were therefore considered to be a compensatory phenomenon (Frey) In some cases, however, the depressing effect, upon the idioventricular rhythm, of the extrasystoles predominates to such an extent that long periods of ventricular standstill with loss of consciousness ensue (Cohn and Lewis, Hecht), particularly if groups of successive extrasystoles occur, so that this mechanism has to be included amongst the rarer causes of Adams-Stokes attacks.

The increase in the degree of block in cases of partial heart block resulting from auricular

extrasystoles is mentioned in the appropriate section (p 55) The rare instances of interpolated ventricular extrasystoles in complete A-V block are discussed in the section on interpolated extrasystoles.

SUMMARY

If ventricular extrasystoles occur in complete A-V block, the conditions differ from those present in the more common kinds of ventricular extrasystolic arrhythmias as both the extrasystoles and the automatic beats of the dominant rhythm originate in the same part of the heart. In such cases the post-extrasystolic intervals equal or closely approximate the normal cycle length, but, with very rare exceptions, are not compensatory The exact length of the post-extrasystolic interval differs in different species and also depends on the experimental conditions Clinically, the occurrence of ventricular extrasystoles in complete A-V block is not uncommon; this is attributable to the fact that the same conditions which are common causes of complete A-V block are also prone to give rise to ventricular extrasystoles. As a rule, such extrasystoles tend to increase the low ventricular rate, but in some cases *their depressing effect upon the idioventricular rhythm is so pronounced that long periods* of ventricular standstill ensue and this mechanism has to be included amongst the rarer causes of Adams-Stokes attacks

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on the differentiation between automatic and extrasystolic impulse formation (*see* p. 492), is in accordance with experimental findings on the activity of several centres of impulse formation in the ventricles after severing both branches of the bundle of His (Wilson and Herrmann) Clinically, the combination of complete or partial A-V block with bundle branch block is by no means uncommon In such cases both bundle branches are affected, the A-V node and main bundle being found normal histologically. This localization of degenerative lesions is due to the fact that the A-V node and bundle derive their

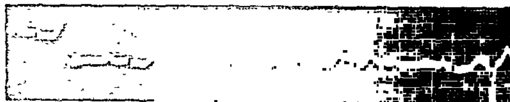


FIG. 73—Lead 2 Ventricular extrasystoles in complete A-V block with lengthening of the post-extrasystolic periods.

blood supply from a source different from [illegible] of the blood supply of the bundle branches ([illegible], Cornell and Claytor) The presence of [illegible]tive foci in both main branches renders [illegible] prognosis more grave.

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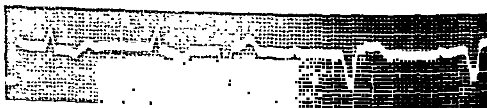


FIG 74—Lead 2. Ventricular extrasystole in complete A-V block, followed by automatic ventricular beats of the same shape as the extrasystole, indicating change in the site of origin of the idioventricular beats.

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extrasystoles is mentioned in the appropriate section (p 55). The rare instances of interpolated ventricular extrasystoles in complete A-V block are discussed in the section on interpolated extrasystoles.

SUMMARY

If ventricular extrasystoles occur in complete A-V block, the conditions differ from those present in the more common kinds of ventricular extrasystolic arrhythmias as both the extra-

post-extrasystolic interval differs in different species and also depends on the experimental conditions. Clinically, the occurrence of ventricular extrasystoles in complete A-V block is not uncommon; this is attributable to the fact that the same conditions which are common causes of complete A-V block are also prone to give rise to ventricular extrasystoles. As a rule, such extrasystoles tend to increase the low ventricular rate, but in some cases their depressing effect upon the idioventricular rhythm is so pronounced that long periods of ventricular standstill ensue and this mechanism has to be included amongst the rarer causes of Adams-Stokes attacks

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EXTRASYSTOLES IN A-V RHYTHM. RETURN EXTRASYSTOLES

Return extrasystoles are produced by an excitation wave which spreads from one chamber of the heart to another, returns to that portion of the heart in which the impulse had first originated and proceeds to give rise to a further systole This phenomenon has been observed mainly in A-V rhythm with preceding activation of the ventricles, in which the stimulus originated in the ventricular portion of the A-V node thence activating ventricles as well as auricles, and that portion of the impulse which activates the auricles returning, or sending a subsidiary impulse back, to the ventricles Similarly, a ventricular extrasystole, which is reversedly conducted to the auricles, may give rise to a return extrasystole, by the return of the impulse to the ventricles, probably in or near the A-V node.

Experimental studies relating to return extrasystoles are intimately connected with those concerned with the effect of extrasystoles upon A-V rhythm, and it seems appropriate first to discuss this latter subject and subsequently to proceed to that of return extrasystoles

Ventricular or Auricular Extrasystoles in A-V Rhythm

Hering (1910) was the first to investigate the effect upon A-V rhythm of ventricular and auricular extrasystoles in the mammalian heart Changes in the sequence of, and time intervals between, auricular and ventricular contractions were interpreted as indicating a shift in the pacemaker, but since only mechanical records were obtained his investigations are mainly of historical interest The same can be said about that part of Ganter and Zahn's extensive investigations on A-V rhythm which deals with the effect of extrasystoles.

Rothberger and Winterberg's investigations carried out in 1912 marked a considerable advance In their experiments on dogs these authors recorded electrocardiograms, in addition to mechanical records of auricle and ventricle; moreover, the conditions of their experiments were far more physiological than those of Hering Whereas the latter author produced A-V rhythm by scorching the sino-auricular node, Rothberger and Winterberg obtained it by stimulating the left accelerans nerve. The main results of their experiments were to determine that after one or several *ventricular* extrasystoles the post-extrasystolic intervals tended to be compensatory. Occasionally intervals shorter than compensatory were observed Even in cases in which ventricular extrasystoles were reversedly conducted to the auricles compensatory post-extrasystolic intervals occurred This latter observation was difficult to understand since it has to be assumed that during its retrograde conduction the extrasystolic impulse passed the A-V node, there destroying the next immature impulse and producing a permanent shift of rhythm. The preservation of the original A-V rhythmicity in spite of a retrograde ventricular extrasystole was then considered to be due, either to the fact that the extrasystole failed to reach the centre of stimulus formation in the A-V node (this being " protectively blocked "), or that it produced inhibition of the formation of the next A-V impulse. Rothberger and Winterberg considered the second alternative as far more likely. In the experiments with *auricular* extrasystoles those which were *not* conducted to the ventricles did not affect the A-V rhythm, and the post-extrasystolic intervals in the auricular rhythm were therefore compensatory. If auricular extrasystoles were produced which *were* conducted to the ventricles, the post-extrasystolic intervals of the ventricular

rhythm either equalled the normal cycle length or, owing to inhibition of the formation of the next A-V impulse, were longer than the normal cycle length, but not compensatory: in both cases the conducted auricular extrasystole passed through the A-V node and thereby produced a permanent shift of rhythm

The use of the word "compensatory", to describe the length of the post-extrasystolic interval in arrhythmias of this kind, might well be considered "unfortunate", as Lewis, White and Meakins pointed out in a similar context. For restoration of the original rhythm, if it occurs, "comes about in a totally different manner to that described by Engelmann, in observing the effect of ventricular extrasystoles upon S-A rhythm". It would not be due to the control of the post-extrasystolic interval by a dominant rhythm, but to a balance between the lengths of coupling and post-extrasystolic interval respectively, such balance being largely coincidental.

Lewis, White and Meakins reinvestigated this problem on a large scale in experiments on dogs in which A-V rhythm was produced by cooling the *sulcus terminalis*; both vagi were cut. In their experiments the type of A-V rhythm was the one with preceding activation of the auricles, P waves preceding the QRS complexes In connexion with the subject of the present section their most important findings were: With *ventricular* extrasystoles, which in most instances were conducted to the auricles, the post-extrasystolic interval in the ventricular rhythm exceeded that in the auricular rhythm by the sum of the R-P interval of the extrasystole and the P-R interval of the post-extrasystolic A-V beat. The post-extrasystolic interval in the auricular rhythm would accurately represent the interval between the disturbance of the A-V impulse formation by the extrasystole and the completion of the next A-V impulse "if conduction is at the same rate from node to auricle for the two beats which bound it". Any divergence should be expected to be in the direction of shortening since, owing to its prematurity, the R-P interval of the extrasystole should be relatively longer. Actually, with one exception, the post-extrasystolic interval in the auricular rhythm was longer than the normal P-P cycle length. With *auricular* extrasystoles the post-extrasystolic intervals in the ventricular rhythm had approximately the same length as the R-R cycles of the A-V rhythm, but usually were slightly longer and only exceptionally shorter. From these observations, particularly those regarding the length of the post-extrasystolic intervals in the ventricular rhythm after auricular extrasystoles, Lewis, White and Meakins drew far-reaching conclusions: they doubted the validity, in such cases, of Wenckebach's views about the paramount importance of the speed of conduction of the excitation in accounting for

sino-auricular rhythm Lewis and his collaborators, who did not consider disturbances of conduction in the bundle of His as a possibility, argued that, if Wenckebach's views were applied in regard to the post-extrasystolic intervals in A-V rhythm, those of the ventricular rhythm after auricular extrasystoles should either equal, or be shorter than, the R-R interval of the A-V beats, but not be longer as was mostly the case

This objection was proved to be invalid, and conditions prevailing in extrasystolic arrhythmias in A-V rhythm were further clarified, by the work of Scherf and Shookhoff (1925) In their experiments on dogs A-V rhythm was produced by severing both vagi and

so as to facilitate the appraisal of the kind and degree of changes in rhythm Extrasystoles were produced by induction shocks

Fig 75 provides an example of such an experiment. The first three beats show A-V rhythm with simultaneous activation of auricles and ventricles, the P waves being buried

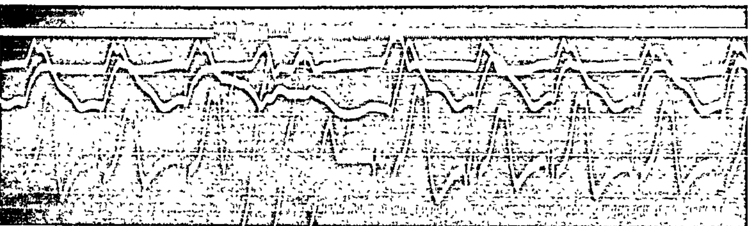


Fig 75—From an experiment on a dog From above downward Signal (electrical stimulation), suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base (0 02 second) The first three beats are A-V beats with simultaneous activation of auricles and ventricles After three ventricular extrasystoles elicited by induction shocks inverted P waves appeared before the QRS complexes of the following A-V beats Gradual restoration of the previous condition

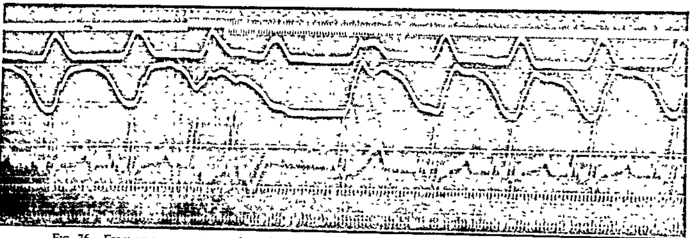


Fig 76—From an experiment on a dog Significance of the several tracings as in previous figure. Temporary disappearance, after two ventricular extrasystoles, of P waves in A-V rhythm.

in the ventricular complexes After three ventricular extrasystoles, the first two of which the suspension curves show to have been conducted to the auricles whereas the last one remained confined to the ventricles, the first post-extrasystolic beat shows an inverted P wave preceding the QRS complex at almost a normal P-R interval In the following beats the inverted P waves gradually approach the ventricular complexes until the former state of simultaneous activation is re-established. Fig. 76, taken from another experiment, shows in the first two beats A-V rhythm which differs from that illustrated in the preceding Fig in that the auricles are activated first, P waves preceding the QRS complexes. Two ventricular extrasystoles are shown which were both conducted to the auricles In the first post-extrasystolic beat no P wave is visible, which indicates simultaneous activation of auricles and ventricles, the subsequent beats showing the return of P waves at increasing P-R intervals until the conditions prevailing before the extrasystoles were restored.

Analysis of the records obtained in numerous experiments showed that, in A-V rhythm, a temporary change in position of the P waves relative to the QRS complexes as a result of ventricular extrasystoles is entirely dependent on, and therefore indicates the importance of, speed of conduction in the ventricles of the first few post-extrasystolic impulses, which is itself dependent upon the demands made previously upon the conducting system by the extrasystoles These conditions are diagrammatically illustrated in Fig. 77 In Fig 77a and b A-V rhythm originating in the lower portions of the A-V node is assumed, the ventricles being activated before the auricles, since, regarding the effects of extrasystoles, the same conditions prevail in cases of simultaneous activation of auricles and ventricles, the origin of the impulse assumed to be in the middle portion of the A-V node, these two diagrams illustrate the findings in tracing Fig 75. With these two kinds of A-V rhythm the temporary occurrence of a positive P-R interval after extrasystoles was found only if the last extrasystole was *not* conducted backwards to the auricles (Fig 77a) It could be concluded that this phenomenon is due to delayed conduction of the post-extrasystolic beats (particularly the first one) from the A-V node to the ventricles This is a result of the fact that the last extrasystole, though not conducted to the auricles, had travelled through a portion of the conducting system in the ventricles, thereby shortening the time of recovery of that portion On the other hand, if the last ventricular extrasystole *was* conducted to the auricles (Fig 77b), the time available for recovery of the ventricular portion of the conducting system was not shortened, if anything it was slightly lengthened (owing to some inhibition of impulse formation in the A-V node caused by the traversing extrasystole), and the phenomenon of a temporary shift of the P waves is therefore never observed in such circumstances In cases of A-V rhythm with preceding activation of the auricles, in which a positive P-R interval is present and the impulse is assumed to originate in the upper portions of the A-V node, the conditions governing a temporary shift of the P waves after ventricular extrasystoles are the reverse of those discussed in connexion with lower and middle A-V nodal rhythm In the diagram Fig 77c and d upper nodal rhythm is assumed, and it is shown that only if the last extrasystole *was* conducted backwards to the auricles will the P wave of the first post-extrasystolic beat temporarily merge with the QRS complex and, in the next few beats, gradually resume its original position (*see* Fig 76) It could be concluded that this is due to the longer time of recovery available for the portion of the conducting system between A-V node and ventricles (*see* Fig 77c) If the last ventricular extrasystole was *not* conducted to the auricles (Fig 77d), the time of recovery of the bundle not only is not longer but shorter, and the first post-extrasystolic impulse will therefore be conducted to the ventricles at the same speed or more slowly, but certainly not faster than before Consequently the moment of activation of the ventricles will not approach that of the auricles, that is, the P-R interval will not become shorter, but will remain unaltered or be lengthened and the phenomenon of a temporary merging of the P waves with the QRS complexes will not be observed All these effects of ventricular extrasystoles in the various forms of A-V rhythm, as well as those of

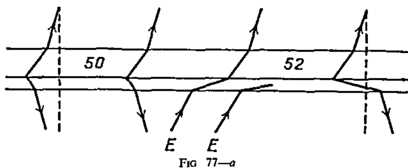


FIG 77—a

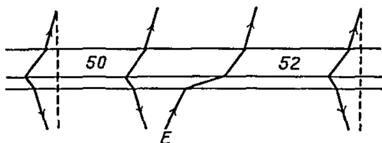


FIG 77—b

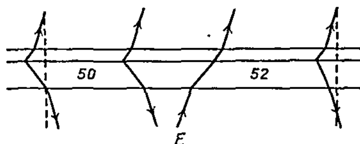


FIG 77—c

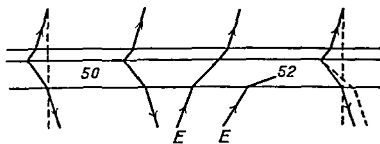


FIG 77—d

FIG 77 —Diagram illustrating the effect in A-V rhythm of ventricular extrasystoles upon the sequence of activation of auricles and ventricles For explanation, see text.

auricular extrasystoles, demonstrated clearly that, contrary to the opinion of Lewis, White and Meakins, "the formulae of rest and recovery or want of rest and recovery" not only fully account for these phenomena, but find a valuable support in the results of such investigations. In A-V rhythm relatively small alterations in the speed of conduction of the impulse to auricles and ventricles result in comparatively large alterations in the time sequence of auricular and ventricular systole, since in A-V rhythm the spread of the excitation wave to those portions of the heart takes place in opposite directions (*see* Scherf and Shookhoff, 1926a). Actually, a temporary change of position of the P waves relative to the QRS complexes, after extrasystoles, is clearly seen in several of the records reproduced by Lewis, White and Meakins, and of Rothberger and Winterberg, but was not commented upon by the writers

Clinically, as far as we are aware, this phenomenon has only once been clearly observed by Edens (his Fig. 12), although differently explained by him. The tracing shows A-V rhythm with inverted P waves preceding the QRS complexes An extrasystole occurred, but it is impossible to decide, from the rather indistinct reproduction, whether it was an A-V extrasystole with preceding activation of the ventricles or a ventricular extrasystole with retrograde conduction to the auricles In the first post-extrasystolic beat no P wave is visible, but reapp[illegible]
being restored w[illegible]
of the paper of [illegible]
in this case

It might be argued that the conditions described in this section are not sufficiently important to warrant a detailed description We make no apology for having done so, for what matters is not the change in the detailed time relations and not whether or where a P wave or any other wave is found in the records, but the knowledge that can be derived from such changes regarding general principles of cardiac physiology and pathology. To quote a few of those points

It could be demonstrated that disturbances of conduction exist in that part of the conducting system which is situated between the A-V node and the myocardium without either of these structures being involved This made it possible to disprove alternative explanations, which had been put forward in order to explain the above described and allied phenomena; for instance, a change in the latency of the A-V node (Mobitz) or of the myocardium (Straub), or of the rate of conduction in the A-V node (Lewis *et al*) The unsatisfactory conception of "shifting of the pacemaker" was proved to be unnecessary for the explanation of such arrhythmias in which this phenomenon was postulated. In addition, Scherf and Shookhoff's work showed the wide range of applicability of Engelmann's and Wenckebach's conceptions of the importance of changes in the rate of conduction of impulses dependent on the period of rest for and recovery of the [illegible]

[illegible]

of, a part of the conducting system Such investigations proved also to be one of the most instructive examples illustrating the great importance of what Engelmann, with such vision, had termed in 1896 the "method of the extrasystoles" (Methode der Extrasystolen), namely, the use of extrasystoles for the elucidation of many diverse problems in cardiac [illegible]

Return Extrasystoles

Experimental Investigations

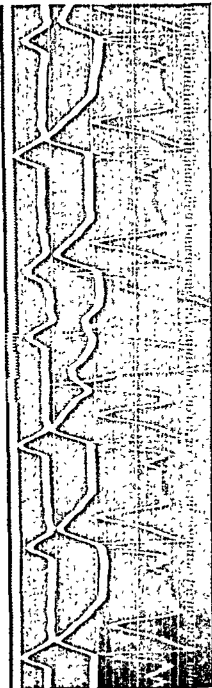


FIG. 78.—From an experiment on a dog. Significance of the several tracings as in Fig. 75. The sixth beat is a return extrasystole precipitated by the preceding ventricular extrasystole. For further explanation, see text.

The subject, which was extensively investigated experimentally by Scherf and Shookhoff (1926b), may be introduced by Fig. 78. A-V rhythm had been produced in the way described above (p. 103). The first three beats are A-V beats with preceding activation of the auricles, diphasic and widened P waves preceding the initial complexes with a P-R interval of 0 11 second The R-R intervals measure about 0 5 second The shape and width of the P waves as well as the notching and widening of the R waves are due to quinine (p 290) These three beats are followed by two ventricular extrasystoles, the second of which is reversedly conducted to the auricles with a V-A interval of 0 22 second. The following beat has in its RS and T portions all the appearances of the initial A-V beats and, calculated from the suspension curves, follows the last extrasystole at about 0·3 second This beat occurs far too early to be of A-V origin, for the interval between the last extrasystole (which by being reversedly conducted to the auricle was bound to destroy, on its passage through the A-V node, the immature A-V impulse) and the following beat should at least equal the R-R intervals of the A-V beats or, owing to inhibition of impulse formation in the A-V node, be longer, but certainly not be shorter. The explanation seems to be that this beat is due to the impulse which precipitated the last extrasystole and which, on its way to activate the auricle, returned to activate the ventricle a second time The presumed mechanism is diagrammatically illustrated in Fig 79 This interpretation is strongly supported by the observation that the premature beats appeared *only* if the ventricular extrasystole, caused by an induction shock, was conducted back to the auricle; if several ventricular extrasystoles occurred this phenomenon was only observed if the last extrasystole was conducted to the auricle. This kind of extrasystole is one variety of what has been termed by the authors return extrasystoles

Another set of circumstances, in which return extrasystoles could be produced in the dog's heart, were certain instances of A-V rhythm with preceding activation of the ventricles, namely, that form in which an inverted P wave follows the QRS complexes In all such

experiments it could be demonstrated that return extrasystoles occurred whenever, and only if, the conduction of the A-V impulse to the auricle was sufficiently delayed for the returning impulse to reach the ventricles after the end of the refractory phase.

Several methods were found effective to produce these phenomena (Scherf, 1941). Fig. 80 provides an example of one of them. A-V rhythm was produced by clamping the sinus node; the suspension curves showed that the auricles contracted at a short interval after the ventricles and in the electrocardiogram inverted P waves followed the QRS complexes. By electrically stimulating the conus of the right ventricle a series of extrasystoles were elicited the last five of which are shown at the beginning of the figure. Subsequently, the retrograde conduction (R-P) intervals alternated between 0·05 and 0·09 second and it can be seen that a premature beat of supraventricular origin occurred only and always with the longer R-P intervals. Within a few seconds longer R-P intervals ceased to occur and premature beats were no longer observed. These findings can be explained by assuming that, as a result of the series of extrasystoles, fatigue of the conducting system ensued, with consequent alternation of the R-P conduction times, and that after the longer R-P intervals the impulse returning from the auricles to the ventricles reached the latter when they had become again excitable. Fatigue of the conducting system by means of auricular extrasystoles had the same result.

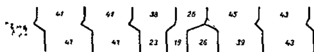


Fig. 79.—Diagram illustrating the mechanism of origin of the beats as recorded in the previous figure.

Fig. 81 illustrates a similar phenomenon. A-V rhythm was produced in a similar manner, that variety being present in which auricles and ventricles are activated simultaneously. Five extrasystoles were elicited in the right ventricle by means of induction shocks. Here again this resulted in an alternation of the ventriculo-auricular conduction times, as shown by the suspension curves; only the beats with the longer V-A intervals were followed not only by one, but by two premature beats. Analysis of the electrocardiogram and suspension curves warrants the conclusion that the first return extrasystole is conducted backwards to the auricles and, as a second return extrasystole, is again conducted to the ventricles. Accurate measurements of the various P-R and R-P intervals are not possible in this record, but approximate figures taken from the suspension curves show that the P-R interval of the first return extrasystole is about 0·24 second, while the conduction time of its reversed conduction to the auricles measures only 0·14 second; the P-R interval of the second return extrasystole is only about 0·13 second. When, after a few seconds, alternation of the ventriculo-auricular conduction times ceased, return extrasystoles failed to occur, but could be made to re-appear several times by again producing series of ventricular extrasystoles by means of induction shocks.

Another method to produce return extrasystoles during A-V rhythm consists in stimulation of the vagus, thereby lengthening the R-P intervals. In Fig. 82, which is taken from such an experiment, the R-P intervals varied between 0·09 and 0·13 second and it can be seen that a return extrasystole occurred whenever the R-P interval exceeded 0·12 second.

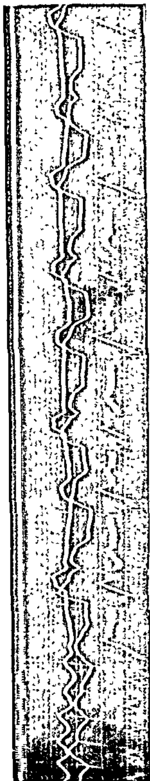


Fig. 80.—From an experiment on a dog Significance of the several tracings as in Fig 75 The beginning of the record shows the last five of a series of ventricular extrasystoles elicited by electrical stimulation of the conus of the right ventricle Subsequently A-V rhythm with alternation of the R-P intervals ensued, those beats with the longer R-P intervals being followed by a return extrasystole.

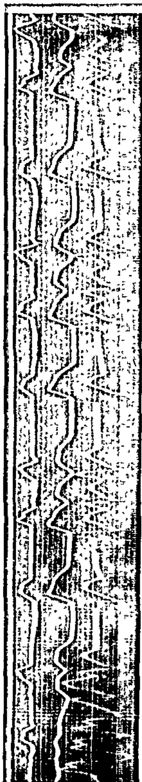


Fig. 81.—From an experiment on a dog Significance of the several tracings as in Fig 75. After a series of ventricular extrasystoles elicited by electrical stimulation of the right ventricle A-V rhythm with alternation of the R-P intervals ensued, those beats with the longer R-P intervals being followed by two return extrasystoles in succession

those beats which were followed by a return extrasystole being indicated by bold figures. Owing to their prematurity the return extrasystoles were aberrantly conducted in the ventricles, as evidenced by their different shape in the electrocardiogram The R-R intervals of the A-V beats following in succession without extrasystoles were 0·60–0·62 second, those containing an extrasystole measured 0·71, 0·70 and 0·69 second respectively, so that the return extrasystoles were interpolated This is only possible if the centre of impulse formation in the A-V node was not affected by the extrasystoles. That this was the case is also proved by the fact that the P-P intervals remained practically the same throughout, varying only between 0 61 and 0 68 second. It has to be assumed that a " protective block " of the A-V centre of impulse formation existed, owing to which the return extrasystoles did not interfere with A-V impulse formation Moreover, this is another instance of an arrhythmia in which the disturbance of conduction is situated in the part of the conducting system between A-V node and ventricle; in the instances of return extrasystoles, conduction through this portion of the system took place three times within a short time and, owing to the inadequate period of recovery, conduction to the ventricles of the post-extrasystolic beat was delayed. This resulted in a shortening of the R-P interval particularly of the first post-extrasystolic beat. The assumption of a conduction of the extrasystole through a different path is not warranted. Failure of auricular stimuli, which are conducted to the ventricles, to disturb the activity of the A-V nodal centre has also been noted by Lewis, White and Meakins, and by Rothberger and Winterberg

Lastly, warming of the A-V node by means of a thermode, or depression of the sinus node by various means elicited return extrasystoles. Here again, these occurred only if the activation of the auricles took place with a sufficient delay after that of the ventricles Thus, with the former method, return extrasystoles were only observed if the R-P intervals measured at least 0 12 second; with the latter, 0 18 second was the shortest R-P interval

appeared exclusively and also constantly when the R-P interval attained a certain length. This finding strongly supports the interpretation given The question arises whether a certain degree of delay in the retrograde conduction to the auricles of A-V beats or ventricular extrasystoles alone gives rise to return extrasystoles, or whether, in addition, fatigue, vagal stimulation and similar factors are necessary; the authors favour the first alternative.

Clinical Observations

In order for a diagnosis of return extrasystoles (reciprocal beats) to be made in clinical cases it has to be ascertained that the auricular contraction, which in its turn gives rise to the second ventricular one, is due to the retrograde activation of the auricles by an impulse which originated in the A-V node (unless the return extrasystole was elicited by a ventricular extrasystole with retrograde conduction to the auricles) This means that the underlying rhythm is A-V nodal rhythm with preceding activation of the ventricles, and that the

sional interference of the A-V rhythm by conducted sino-auricular beats (*see* p. 178, *also* Herrmann and Ashman). In the electrocardiogram a reciprocal beat manifests itself by the presence of A-V rhythm, a P wave which is inverted in leads 2 and 3 following the QRS complex at a certain distance, such P wave being followed in its turn by a supraventricular QRS complex after an interval consistent with the assumption that the second ventricular beat is due to the return of this auricular impulse to the ventricles Such inverted P waves are therefore " sandwiched " in between two supraventricular QRS complexes (White, 1921)

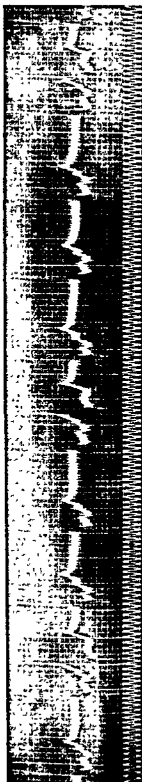


FIG. 82.—From an experiment on a dog A-V rhythm. Those beats which, as a result of vagal stimulation, had a lengthened R-P interval were followed by a return extrasystole

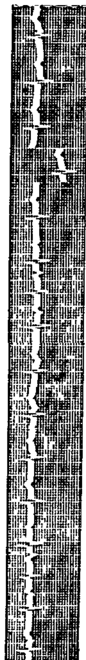


FIG. 83.—Lead 2 A-V rhythm In two places two return extrasystoles in succession (the third and fourth, and tenth and eleventh beats) For further explanation, see text.

Fig 83 provides an example, obtained from a fifty-six-year-old man with coronary sclerosis. The underlying rhythm is A-V rhythm with gradually lengthening R-P intervals During undisturbed A-V rhythm the R-R intervals measured 0·66 second (rate 91), and the record shows that whenever the R-P interval reached 0·22 second the P waves were followed by a QRS complex which, in relation to the underlying A-V rhythm, occurred prematurely There is no evidence in this record of an independent sino-auricular or auricular pacemaker The interpretation that these premature ventricular beats are return extrasystoles is supported by the observation that the speed of orthograde conduction of such beats varied inversely with that of the preceding retrograde one. Thus the R-P interval of the second beat measured 0·22 second, and the P-R interval of the following (conducted) beat 0·28, whereas the corresponding figures of the next beat were R-P· 0 3, P-R· 0 20. The tracing therefore demonstrates return extrasystoles, of which two occurred in succession in two places (the third and fourth, and tenth and eleventh beats) This arrhythmia, due to two successive return extrasystoles, is even rarer than single return extrasystoles, the only reported clinical observation of this kind is Case 5 of Decherd and Ruskin (1943), who termed this sequence " triplets ". Another possible instance is the case of von Dobozy, though differently interpreted by him In his Fig 4 two groups each of three beats were recorded Dobozy's explanation is that the first two beats of each group were an A-V beat with a return extrasystole, the R-P intervals being 0 45 and 0 46 respectively, and that the last beat of each group was a supraventricular extrasystole An alternative and more likely explanation seems to be that each group consists of an A-V beat followed by two return extrasystoles. Such an interpretation would be supported by the presence, between the second and third beats of the first triplets, of a differently shaped inverted P wave, the absence of such a wave at the corresponding place in the second group would not exclude the same rhythm (cf. Cutts' and Levin's findings discussed below) The fact that the P-R intervals (0 16 second) of the last beats of each group were shorter than those of the first return extrasystoles would be analogous to Scherf's experimental findings (*see* Fig 81)

The number of published clinical observations in which the diagnosis of return extrasystoles can be considered established is very small In an extensive review of this problem Decherd and Ruskin collected twenty-two cases up to 1943 to which they added three personal observations The first case was published by White (1915). A-V rhythm was present and whenever, as a result of carotid sinus pressure or the exhibition of digitalis, the R-P intervals were prolonged to about 0 3 second, bigeminy resulted. Amongst various explanations White discussed the mechanism of a return of the impulse The same author reported a second case in 1921, showing a bigeminal action with R-P intervals of 0 4 and P-R intervals of 0·18 The diagnosis, however, seems less certain since the P waves were upright when bigeminy was first observed and, when subsequently they became inverted, bigeminy did not always occur when the R-P interval reached the same length Drury first used the term reciprocal rhythm in a clinical observation, in which he described this rhythm during attacks of A-V tachycardia with incomplete retrograde block and a rate of about 150 Other cases in which this arrhythmia can be considered established are: Bishop, in whose case return extrasystoles occurred after atropine, Gallavardin and Gravier, and Katz and Kaplan who demonstrated transient reciprocating rhythm during carotid sinus pressure; Case 1 of Blumgart and Gargill (although the tracing is too short to be conclusive, [illegible]

years after diphtheria, though not interpreted as such by the author, Cutts, one case, *see* below; Gravier, Froment and Guiran (R-P 0 45, P-R 0 2), though the varying direction of the P waves made some of the tracings difficult to interpret with certainty (*see* below),

Levin (1941), one case, *see* below; Decherd and Ruskin, three cases; Tourniaire, Deyrieux and Augier (observed after every second A-V beat with a R-P interval of 0·3; atropine [illegible]

[illegible] arteriosclerosis; on one occasion two return extrasystoles were recorded, also fusion beats); Bix (Case 3), Holzmann (1952).

Some special features warrant a brief discussion. Generally the R-P (Q-P) intervals were longer than the P-R intervals of the return extrasystole (for instance, White, 1915, Gravier *et al.*, Decherd and Ruskin) which conforms with the observation that, generally, retrograde conduction takes place less readily in the mammalian heart than the orthograde one (*see* "Retrograde Conduction of Extrasystoles", p 126); there are, however, exceptions (for example, Blumgart and Gargill, Case 1). An inverse relationship between the R-P and following P-R intervals seems to be the rule In Decherd and Ruskin's extensive study of one of their cases these time relations were used to determine the curve of recovery of conductivity. This showed the presence of a period of relative refractoriness which resembled recovery curves obtained in experimental work, and in a human case of heart block by Ashman and Herrmann It was also found that, in general, reciprocal beats occurred with longer R-P intervals, which is in accordance with the experimental findings described above, but Cutts pointed [illegible]

[illegible] other factors determine whether return conduction occurs or fails; this recalls similar considerations concerning interpolated extrasystoles (*q.v.*). Cutts also noted that the QRS complex of the second beat of the couple often differed somewhat in shape from the first, which is attributable to aberrant conduction of the second impulse in the ventricles

The spread to the ventricles of a return extrasystole may be completely blocked and its presence is then deduced from the time relations between two successive A-V beats. If such interval without a recorded ventricular contraction of a return extrasystole equals that in which a return extrasystole was recorded in the ventricular rhythm, the assumption is justified that such lengthening in the interval between two successive A-V beats was caused by a return extrasystole which, owing to blocked conduction to the ventricles, failed to yield a ventricular contraction (concealed conduction, Langendorf; Pick and Langendorf; Fleischmann).

Regarding the effect of drugs, digitalis was often noted to cause, or increase the number of, reciprocating beats (White; Dock, Blumgart and Gargill, Case I; Decherd and Ruskin; Cutts) Vagal stimulation by carotid sinus pressure produced transient reciprocating rhythm (Gallavardin and Gravier, Katz and Kaplan) or increased their number (Blumgart and Gargill, Case 1), but in the last case physostigmine had no effect. Statements about the effect of atropine are conflicting in Bishop's case it provoked return extrasystoles and in that of Dock greatly increased their number, the A-V rhythm being accelerated with lengthening of the R-P and slight shortening of the P-R intervals, whereas in Case I of Blumgart and Gargill 2mg completely abolished the return extrasystoles. Cutts found that atropine alone had no constant effect regarding reciprocating rhythm, but in one instance abolished it when given after digitalis According to Decherd and Ruskin grain 1/50 given intravenously accelerated retrograde conduction while producing little effect on the refractory period or forward conduction Quinidine prolonged refractoriness and delayed both retrograde and orthograde conduction

Clinical observations of return extrasystoles elicited by ventricular extrasystoles with retrograde conduction are very rare Fig. 84 provides an example The record was obtained from a seventy-three-year-old patient with hypertension and coronary sclerosis It

shows sinus bradycardia, the R-R intervals measuring 1·02–1·27 seconds (rate: 47–58). Groups of two ventricular extrasystoles are seen, the first, fourth and fifth of which were followed by a compensatory pause The second and third of these groups, on the other hand, were followed by a post-extrasystolic interval which was very much shorter, and in which an inverted P wave is seen The R-P intervals, that is in this case the interval between the beginning of the second extrasystole of the groups and the inverted P wave, measured about 0 4 second, the P-R intervals of the post-extrasystolic beats 0 2 second (equalling that of the sino-auricular ones). The conclusion is warranted that the second extrasystole of the second and third groups were followed by a return extrasystole.



Fig 84.—Lead 2. Return extrasystoles precipitated by a ventricular extrasystole For further explanation, see text.

Fig. 85 provides another example, obtained from a man of forty-three who had a myocardial infarction in the anterior wall. It shows sinus rhythm, the R-R intervals varying between 0 88 and 0·94 second (rate: 63–68) There is evidence of myocardial damage (slight distortion of the R-T segments, sharp inversion of the T waves in leads 1 and 2) In lead 1 the second sinus beat is followed by a ventricular extrasystole with a coupling of 0·46 second; the post-extrasystolic interval is compensatory. After the next sinus beat a ventricular extrasystole with a coupling of 0·44 second occurred which in its turn was succeeded by an abnormal ventricular complex of which it could not be stated whether this was another ventricular extrasystole arising from a different focus or a return extrasystole with aberrant intra-ventricular conduction The interval between the sinus beats preceding and succeeding these two abnormal ventricular complexes measured 1·76 seconds, that is, there was no disturbance in the dominant rhythm. The absence of a P wave before the second abnormal complex is inconclusive since, in auricular or return extrasystoles, they are often very small or absent in lead 1 The nature of this unusual arrhythmia becomes clear from lead 2. The middle of this lead shows a sinus beat followed by a ventricular extrasystole with compensatory post-extrasystolic pause (coupling + post-extrasystolic interval = 1 62 seconds; cycle length of sinus rhythm 0·81 second). The next sinus beat is followed by a ventricular extrasystole with the same coupling (0 45 second) and having the same shape except for an inverted P′ wave being visible in its final deflection After a P′-R interval of 0 28 second this extrasystole was followed by a ventricular complex which differed in shape from that of the sinus beat though having the appearances of a supraventricular beat. The interval between the two sinus beats preceding and succeeding these two abnormal complexes measured 1 80 second and there was thus a shift of the dominant rhythm The interval between the inverted P′ wave of the returning impulse and the P wave of the next sinus beat measured 0 96 second, as compared with the calculated cycle length of 0 81 of the sinus

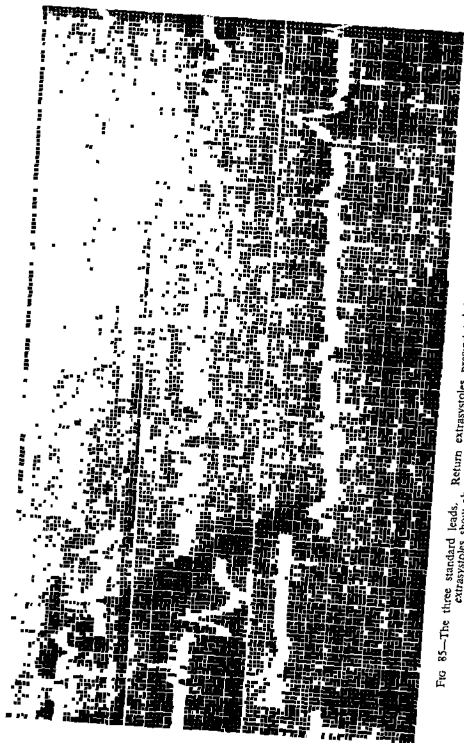


Fig 85—The three standard leads. Return extrasystoles precipitated by ventricular extrasystoles The return extrasystoles show *aberrant intra-ventricular conduction* and reached the sinus node

rhythm. The most likely interpretation of this portion of the record is that the second abnormal ventricular complex was a return extrasystole with aberrant intra-ventricular conduction, which reached the sinus node and which was precipitated by the ventricular extrasystole The first sinus beat in lead 2 is also followed by a ventricular extrasystole with a coupling of 0 44 second It shows the same kind of inverted P' wave in its final deflection as the third extrasystole, but this is not followed by a ventricular complex and there is no shift of the sinus rhythm The inference is that this extrasystole too returned to activate the auricles, but the impulse failed to reach either the sinus node or the ventricles: return extrasystole with blocked ventricular conduction

The only other clinical observations of this phenomenon, of which we are aware, are those of Levin (1941), Schott (1951) and Kistin and Landowne

Levin's case is unique in that return extrasystoles were precipitated by both A-V beats and ventricular extrasystoles with retrograde conduction to the auricles Apart from this, his report is of interest in several other respects The patient gave a history of rheumatic fever at the age of twenty-one and of an "infection of the legs" in the following year Several years later numerous electrocardiograms were taken during broncho-pneumonia with pleurisy (Levin and Ochoa), which showed an unusual variety of arrhythmias, namely, sinus tachycardia, auricular flutter, A-V rhythm with bundle branch block, dissociation with interference and isorhythmic dissociation This was attributed to a toxic effect of the acute infection upon the conducting system previously damaged by rheumatic fever. Subsequently (Levin, 1940) reciprocal rhythm was found amongst various other arrhythmias, including dissociation with interference Further studies of the reciprocal rhythm originating from the A-V node showed the unusually long retrograde conduction times of 0 6–0 75 second, the forward conduction times being 0·30–0 35 second The R-P interval of the ventricular extrasystoles with retrograde conduction was shorter (0 5 second) than that of the A-V beats, which at first sight is surprising, since the path of retrograde conduction of ventricular extrasystoles obviously is considerably longer than that of beats originating in the A-V node Levin puts forward good reasons for attributing this phenomenon to facilitation (Bahnung)* of retrograde conduction of the ventricular extrasystoles by the preceding beat (whether of A-V or S-A origin), since the ventricular extrasystoles which gave rise to return beats followed the preceding beats at relatively shorter intervals than did those of A-V origin (Skramlik, 1920a, *see* also p 126, "Retrograde Conduction of Ventricular Extrasystoles") Another interesting observation in his case, previously made by Cutts, was that occasionally coupled beats, of the same time sequence and shape in the electrocardiogram, occurred as unquestionable return extrasystoles, but without a P wave being visible between the two ventricular complexes forming the couple. This is interpreted as indicating that return extrasystoles may be produced by an impulse originating in the A-V node, which activates the auricles and returns to the ventricles, without giving rise to an auricular systole which therefore does not seem to be indispensable in the production of reciprocating rhythm It seems even possible that in such cases the impulse returns in, or in the vicinity of, the A-V node without activating the auricles

The observation reported by Schott (1951) was made in a man of fifty-two who, during convalescence from acute glomerulonephritis, developed an acute pyelonephritis which is a very unusual combination During that period an extrasystolic arrhythmia was recorded mostly presenting as trigeminal rhythm, two ventricular extrasystoles following in succession. On several occasions the second extrasystole of such groups was followed by a supraventricular complex which could be shown to be a return extrasystole precipitated by the second extrasystole. The time relations indicated that the impulse was conducted in a retrograde direction as far as the S-A node, with consequent shift of the dominant rhythm.

* For definition of this term, see p 136



Fig. 86.—Lead 2. Most probably sino-auricular block with escaped beats, simulating return extrasystoles, but possibly return extrasystoles with alternation of pathway of activation of auricles. Time base 0.2 second.

In one instance a return extrasystole with blocked ventricular conduction had to be assumed. In some respects this observation resembled that illustrated in Fig. 85.

The important recent paper by Kistin and Landowne, which contains at least one instance of return extrasystoles precipitated by ventricular extrasystoles with retrograde conduction to the auricles, is discussed in some detail in the section on "Retrograde Conduction of Ventricular Extrasystoles" (p. 126).

While in cases of A-V rhythm with supraventricular premature beats, in which reciprocating rhythm is considered, sharply inverted P waves in leads 2 and 3 form the rule, the varying in shape of such P waves and even alternation in direction do not exclude such a possibility. Decherd and Ruskin have published several instances of such an arrhythmia in which two retrograde P waves, sometimes of varying shape, were found with one A-V beat, the first indicating very rapid retrograde conduction and the second, with a considerably longer R-P interval, giving rise to reciprocation. This is considered by these authors as indicating a double auricular pathway, resulting in two activations of the auricles by the same A-V impulse, the second of which gives rise to a return extrasystole.

A personal observation seems to illustrate the possibility of such a variation in the direction of auricular activation in a case of return extrasystoles. A series of five coupled beats is shown (Fig. 86), the first of each couple being of A-V origin. Between the first and second beat of each couple a P wave is recorded which is alternately inverted and upright. The inverted P waves follow the preceding QRS complexes with a R-P interval of 0.48 second and, in their turn, are followed by a supraventricular complex with a P-R interval of about 0.2 second (the first, third and fifth couple). In the second and fourth couples, on the other hand, the P waves are upright, the R-P intervals being 0.4 and the P-R intervals being 0.3 second respectively. The most likely explanation of this tracing, taken by itself, would be return extrasystoles with alternation of the pathway of activation of the auricles. This interpretation would be supported by the observation that the inverted P waves are constantly associated with longer R-P and shorter P-R intervals than the upright ones, and that there is an inverse relation between the R-P and P-R intervals. On some occasions, only inverted P waves were recorded, which also accords with this interpretation. Many other tracings of this patient, however, which were published (Scherf and Shookhoff, 1926b, Fig. 13, Wenckebach and Winterberg, 1927, Figs. 339, 340, 342, 343) showed sino-auricular block over long periods. If, in this arrhythmia, automatic ventricular escape beats occur, followed by sinus beats at varying intervals, the P-R intervals of the sinus beats are known to vary and to show also the inverse relationship between the R-P and P-R intervals. The alternative explanation of the reproduced record offers itself, therefore, that it indicates sino-auricular block with escape automatic ventricular beats. The varying shapes of the P waves

would not, in this case, be against this diagnosis since this is a common occurrence in sino-auricular block, and even during regular sinus rhythm records of this patient showed continual changes in the shape, and often inversion, of the P waves due to aberrant intra-auricular conduction This record illustrates that, if taken by itself, no objection could be raised against a diagnosis of return extrasystoles with alternation of the pathway of activation of the auricles, whereas the alternative diagnosis of sino-auricular block with ventricular escape is equally well founded when the other records of the same patient are given due consideration A decision between these two possibilities cannot be made with certainty and this instance provides an instructive example how fallacious the interpretation of short records of more complicated arrhythmias is likely to be

In addition to the cases discussed so far others have been reported in which we consider the diagnosis of return extrasystoles questionable Those published before the advent of electrocardiography cannot be accepted as established (Wenckebach, Muskens). Other cases which we consider doubtful are Jones and White, Wolferth and McMillan· their statement that in their Case 2 a 2 1 block was present is not acceptable, as stated on p 134 (retrograde conduction in A-V block), and therefore their conclusion of a reciprocal beating auricle-ventricle-auricle is invalid; Blumgart and Gargill (1930), Cases 2, 3 and 4; Fogelson (the short indistinct records are inadequate for interpretation), Korth and Schrumpf (in Case 1, the diagnosis is certainly erroneous, in Case 2 possibly correct, but not proven), Bain (as far as ascertainable in the short reproduced record there was an independent auricular rhythm), Langendorf, Katz and Simon (1944) whose case was, in our opinion, one of interpolated ventricular extrasystoles, the varying shape of the P waves of some of the post-extrasystolic beats being due to slight variations in the position of such waves in relation to the preceding T waves on which they were superimposed, Mesquita (Case 3, more likely conducted beats during supernormal phase of A-V beats; Case 4 more likely interpolated ventricular extrasystoles, Case 5 coronary sinus rhythm with Wenckebach periods), Bix (Case 2, blocked and conducted auricular extrasystoles whereby the post-extrasystolic beats have P waves of the same abnormal shape as the extrasystoles)

Longer periods of reciprocal rhythm in clinical cases have been reported by Fischer, and by Samojloff and Tschernoff In Fischer's case attacks of tachycardia occurred which were initiated by an A-V extrasystole His interpretation of the records is that the extrasystole resulted in a delay of the activation of the ventricles by the subsequent supraventricular impulse and that, for this reason, the ventricular impulse was reversely conducted to the auricles, which it reached outside their refractory period and in this way a ...
rhythm is supposed to have ensued
the ventricular contraction to spread
far more likely explanation. Samojloff and Tschernoff interpret some of their tracings as indicating the simultaneous presence of two reciprocating rhythms, one originating from an A-V beat and the other from an extrasystole with retrograde conduction The possibility of such an occurrence is admitted, but cannot be considered proved In the case published by Naim as an instance of paroxysmal tachycardia due to reciprocal rhythm there is the alternative possibility that the arrhythmia was paroxysmal auricular tachycardia with blocking of some of the auricular extrasystoles A similar ...
the case of Codina-Altés an
which have been reported c
auricular extrasystoles and paroxysmal auricular tachycardia is an alternative and more likely explanation

In the differential diagnosis of cases of suspected return extrasystoles the main difficulty consists in distinguishing this arrhythmia from dissociation with interference or auricular parasystole As mentioned above, the deciding factor is whether or not there is evidence of an independent rhythm activating the auricles. As in so many arrhythmias, only longer

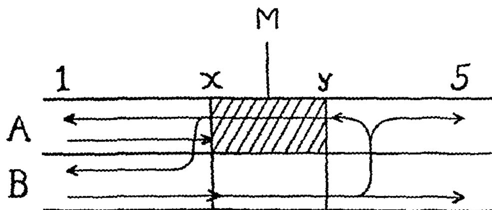
records allow a diagnosis to be made with any degree of certainty Luten and Jensen stressed the importance of auricular parasystole in the differential diagnosis. Zeisler pointed out that many cases considered to be examples of reciprocal rhythm actually were cases of dissociation with interference, but seems to have gone too far in his rejection of the former diagnosis the reverse mistake is also not unlikely, for an independent auricular pacemaker may be simulated in cases in which A-V rhythm with a fairly constant R-P interval and reciprocal beats is present (Decherd and Ruskin). A case interpreted as dissociation with interference and intra-auricular disturbances of conduction, simulating in parts reciprocal beats, has been reported by Schott (1937). Both conditions were present in the same patient at different times in Levin's case (1941) discussed above.

Physiological Considerations

Experimentally the re-activation of auricles and ventricles by the same impulse was first described by Mines (1913) in the electric ray and frog. " after the application of rhythmic stimuli at some particular rate, the cessation of the stimuli was followed by a quick reciprocating movement of the auricle and ventricle or of ventricle and bulbus. The appearance of the heart gave the impression that the beats of the ventricle were caused by those of the auricle and bulbus, while these in turn were caused by the ventricle ". This reciprocating rhythm could be stopped by a properly timed induction shock Subsequently, Mines (1914) amplified these experiments on portions of auricle and ventricle of the tortoise, rings cut out from auricles of elasmobranch fishes and of ventricles of large dogs and cats. It will be noted that the clinical observations on return extrasystoles, as well as the electrocardiographic findings discussed earlier in this section, differ from Mines' result in that only one, or at most two, return extrasystoles were seen, whereas in Mines' experiments and those of Garrey, both of which form the basis of the theory of circus movement, such rhythms lasted for considerable periods. In order for a reciprocating rhythm to be possible it has to be assumed that part of the tissue is in a refractory state at a time at which normally it would be excitable This results in a delay of conduction as well as in changes in the path of the excitation which, owing to the presence of islets of refractory tissue, pursues longer and more devious routes " The excitation wave in travelling through muscle in this state will be delayed in journeying between given points, since it will swerve from side to side as it passes through the only channels open to it The degree in which it swerves may be so great that it reaches muscle at a greater distance before it reaches, by returning, muscle lying at a shorter distance from its starting point " (Lewis)

A return of the excitation wave as a result of the presence of refractory tissue, which is implied in these words of Lewis, was experimentally established by Schmitt and Erlanger on strips of ventricular muscle of the turtle; their work also demonstrated that the return of the excitation wave depended on the presence of unidirectional block, that is, of the presence of tissue in such a high state of refractoriness that conduction in one direction failed. In their experiments strips of ventricular muscle were mounted through five chambers which were divided by rubber curtains, and conduction was depressed by electrical polarization, cold and alteration in the ionic balance (KCl, withdrawal of Ca), also locally by the pressure of the dividing rubber curtains The degree of impairment of conduction proved to be unequal according to the direction in which the excitation was made to spread through the strip (called heterodromia), reaching the degree of unidirectional block in which a stimulus was blocked in one direction while being conducted in the opposite one (called monodromia) In eleven experiments it was found that, when heterodromia of such a degree that it bordered on monodromia was present, the impulse, after having traversed the strip in one direction, returned to excite a second time that part of the strip from which it had originated. This is explained by the assumption, diagrammatically illustrated in Fig 87, that, in the zone of depressed conduction, only a fraction of the fibres conduct the impulse,

and this at a reduced speed, whereas the remaining fibres, in which conduction is even more impaired, fail to conduct altogether in the original direction, impairment of conduction having reached the stage of unidirectional block (monodromia). After reaching normally excitable tissue beyond the zone of impairment, the impulse turns back and passes through those fibres which, not having conducted in the original direction, are excitable and conduct the impulse in the opposite direction, so that it subsequently reaches the excitable tissue again from which it originally started Schmitt and Erlanger applied these findings to explain certain varieties of extrasystoles. They argued that, if an area of depressed conductivity is assumed to be present in an ultimate twig of the conducting system, there producing locally unidirectional block in the direction from conducting system to myocardium, the excitation wave would enter the nearby myocardium from the penultimate twig only by

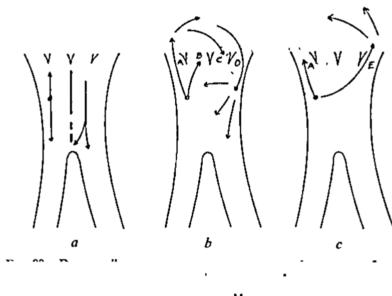


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extrasystoles for reasons which will be discussed in the appropriate chapter (pp 483–4). Their experiments are, however, of great importance for the understanding of return extrasystoles. Similar observations on "reflected" excitation waves travelling in a direction

There is no doubt that this particular variety of extrasystoles is due to a re-entry mechanism Applying Schmitt and Erlanger's findings, Scherf (1941) postulated a functional longitudinal dissociation of some of the auriculo-ventricular conducting system, whereas the part just above the bifurcation may be employed by both the A-V beat and by the return extrasystole to which it gave rise (*see* Fig 88a). The numerous fibrinous septa between the strands of the specific system may facilitate such dissociation Decherd and Ruskin, in

order to explain certain of their observations discussed above, have modified this conception by assuming " an area of refractory tissue of varying size and shape, and/or varying stages of recovery ", situated at the junction of the atrial and ventricular portions of the A-V node or perhaps near the junction of the nodal tissue and auricle (*see* Fig. 88b and c). If an impulse spreading along pathway A encounters an area of relative refractoriness, its conduction will be delayed Assuming further an area of greater refractoriness in area B, blocking the spread of the impulse in this direction, this and the adjacent area C will have been rendered completely refractory for a time by the blocked impulse and therefore will block the passage of an impulse in the direction to the ventricles. If, however, the delay of conduction through area A is sufficiently great for some part of the adjacent area to have regained excitability at the time when the impulse has penetrated the area A, the impulse will be capable of spreading through excitable tissue to the region below the A-V node Owing to the delay of its spread in the retrograde direction through A, and perhaps also of that in the orthograde direction through the partially recovered portion of area BCD (Fig. 88b), this impulse will reach the ventricles outside their refractory period and thus produce



the extrasystole This conception would also afford an understanding for the double auricular pathways. variations in the size and shape of the area of refractoriness could allow rapid retrograde conduction of the impulse through one pathway, say A (Fig 88b and c), with sufficient time for the auricle to respond to a second A-V impulse being conducted with a considerable delay through another pathway, say B or E, this second impulse producing a second auricular contraction and subsequently re-entering the infranodal tissue by forward conduction, as in the previous example.

These two views have the essential conception in common that they postulate an area of refractoriness in the vicinity of the A-V node, in the neighbourhood of which the impulse returns, or sends back a subsidiary impulse, to the ventricles Scherf's conception places it in a longitudinal direction through the node itself, whereas Decherd and Ruskin think of it as a more extensive area, varying in shape and size, situated more towards the auricle. The exact localization of the area of dissociation, or refractoriness, probably varies in different cases Decherd and Ruskin emphasize that in the majority of cases the returning impulse

discharges the nodal pacemaker and from this, as well as from several other features of their records, conclude that the same tissue is affected by the impulses going in the two directions The inverse relationship between the P-R and R-P intervals of the return extrasystoles strongly suggests that, at least for part of their path, the two impulses employ the same channels That this is not the explanation of all the cases is proved by the observation that return extrasystoles may be interpolated (*see* Fig 82), and Decherd and Ruskin concede that, for at least these cases, some kind of dissociation or protective block of the A-V pacemaker has to be postulated In the absence, so far, of histological reports of cases known to have shown return extrasystoles these views are necessarily speculative, but it should be recalled that Ashman and Hafkesbring's experiments on asymmetrical compression have demonstrated the importance of the shape of damaged tissue in the production of unidirectional block (*see* p 134), and the very few histological reports on cases having shown retrograde conduction in complete A-V block seem to emphasize the importance of the site of the lesion Only when histological findings in cases of return extrasystoles become available will it be possible to pronounce a more definite judgment about the nature, site and boundaries of the lesion, giving rise to this rare arrhythmia The salient fact at this stage of our knowledge is that it constitutes a variety of extrasystoles which are unquestionably due to a re-entry mechanism

In view of the small number of observations nothing can be said about any special clinical significance of return extrasystoles However, perusal of the literature shows that a great proportion of such patients were suffering from pronounced structural heart disease (and were under the influence of drugs) Considering that, in the vast majority, the underlying rhythm was A-V nodal rhythm, this observation accords well with that of Ruskin, McKinley and Decherd (1945) that amongst forty-five patients showing A-V nodal rhythm no fewer than 80 per cent had demonstrable heart disease The further findings of these authors that A-V rhythm occurred in only 0 45 per cent of ten thousand patients of their Heart Station and that amongst their forty-five patients with A-V rhythm only three showed the variety with preceding activation of the ventricles, which alone gives rise to return extrasystoles, bring out an important reason for the great rarity of this arrhythmia

SUMMARY

If, in experimental work, A-V rhythm is produced and auricular or ventricular extrasystoles are elicited, certain alterations in the time sequence between auricular and ventricular systole occur temporarily in the first few post-extrasystolic beats Such changes were observed only in certain analysable conditions and it could be shown that they were due to disturbances of conduction in the main bundle of His, which did not affect either the A-V node or the myocardium As, in A-V rhythm, the impulses activating auricles and ventricles respectively travel in opposite directions, relatively small changes in the speed of conduction in either direction result in comparatively large alterations in the time sequence between auricular and ventricular activation, for this reason A-V rhythm lends itself particularly well to investigations of this kind. The importance of these findings in connexion with fundamental properties of cardiac physiology and pathology is discussed Clinically, this phenomenon was observed with certainty in only one case

If, during A-V rhythm with preceding activation of the ventricles, the activation of the auricles is delayed beyond a certain measure, a return extrasystole may result by the return of the excitation wave, in or close to the A-V node, towards the ventricles, the same impulse thus activating the ventricles a second time The degree of delay in the activation of the auricles necessary for this phenomenon to occur varies in different experimental and clinical conditions. In a similar manner return extrasystoles may also be precipitated by a ventricular extrasystole with retrograde conduction to the auricles Various methods of

producing return extrasystoles experimentally are described The literature on clinical observations showing this phenomenon is critically reviewed, and the differential diagnosis is discussed with special reference to distinguishing this arrhythmia from dissociation with interference and from auricular parasystole Hitherto unpublished examples of two successive return extrasystoles, of return extrasystoles precipitated by ventricular extrasystoles with retrograde conduction to the auricles, and of return extrasystoles possibly illustrating varying paths of auricular activation are reported. The occurrence in man of a persistent reciprocating rhythm, entailing more than two successive return extrasystoles, cannot be considered as established.

In order for a reciprocating rhythm to be possible a unidirectional block has to be postulated, resulting from the presence, in or near the A-V node, of refractory tissue which is responsible for the delay in, and the abnormal direction of, the spread of impulse. As the salient point it is emphasized that reciprocating rhythm (return extrasystoles) can be considered as unquestionably being due to a re-entry mechanism, but that this mechanism is not acceptable as an explanation for all, or even the majority of extrasystoles.

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RETROGRADE CONDUCTION OF VENTRICULAR EXTRASYSTOLES TO THE AURICLES

It would be surprising if, as believed until recently, in man ventricular extrasystoles were only rarely conducted to the auricles, since, both in muscle and nerve, impulses are known to travel in both directions and in many animals the conduction of impulses from one part of the heart to another is by no means confined to one direction.

Experimental Observations

In the heart of Ascidiae the sequence of contractions of the various portions normally reverses its direction periodically (Gaskell, 1883), the heart of certain fish shows a "disposition" to reverse the order of contraction (ref *see* Skramlik, 1927a), and by a single mechanical stimulus applied to the *conus arteriosus* of the heart of the skate the normal sequence of contraction can be reversed for several minutes, while the normal order can just as easily be restored by a gentle stimulation of the sinus end (Gaskell, 1883). In the heart of certain species of fish retrograde conduction takes place faster and with greater ease (also persists longer in the dying heart) than orthograde one (Carlson, v. Skramlik 1924, 1927a, 1930), *though recently Kisch (1948) has cast doubt upon whether this holds good as a general rule:* in electrographic investigations he found that the A-V conduction was slower than the V-A one in only two out of nineteen experiments and that the relations between the speeds of retrograde and orthograde conduction depended on the site at which the extrasystole was produced.

Concerning the amphibian heart, reversal of the normal order of contraction in the frog's heart was first reported in 1850 by Hoffa and Ludwig after application of tinct opii to the septum, stimulation of the ventricle produced ventricular contraction followed by that of the auricles and bulbus.

Engelmann (1895, 1896) pointed out that conduction in only one direction depended, *inter alia*, on the speed of change of those physiological conditions which acted as the stimulus and that in the frog's heart three different kinds of fibres were involved (atrial, connecting fibres and ventricular) which differed in the speed of their contractions and conduction.

If, during the passing of the impulse from one category of fibres to another, the impulse meets fibres which, by virtue of their inadequate speed of conduction, do not respond to the oncoming stimulus, its conduction is blocked, and since the connecting fibres have the lowest rate of conduction, it is here that the propagation of the impulse ceases, for this reason Engelmann termed the connecting fibres "Blockfasern" (blocking fibres) By differences in temperature or the application of poisons (veratrine) he was able so to alter conduction in the frog's sartorius (where normally it is equal in both directions) that conduction in one direction was abolished, whereas that in the reverse remained intact, thus imitating, to a certain extent, the conditions found in the heart. From these experiments Engelmann drew far-reaching conclusions about the myogenous nature of the propagation of the cardiac impulse, the validity of which was later queried by Skramlik (1920b)

Skramlik, who carried out extensive investigations on the retro- and orthograde conduction in the frog's heart, found that, unless special circumstances are present, conduction between two parts of the heart is unequal and faster in the normal (sinus-auricles, auricles-ventricle, ventricle-bulbus) than in the reverse direction To a certain extent this is probable even in the ventricle, where apex-base would be the normal direction. By various means it is possible, not only to abolish retrograde conduction, but also to block exclusively the orthograde one conduction only in the normal direction was preserved if all connexions between auricles and ventricle were severed except a narrow dorsal bundle, or if the ventral communications were damaged by heat while the dorsal portions were protected by cooling On the other hand, if the septum alone was left intact, only the retrograde conduction remained Skramlik concluded that the septum mediates the retrograde conduction, whereas certain dorsal bundles effect exclusively or predominantly orthograde conduction; the ventral and lateral bundles are concerned with both (Skramlik, 1920b).

If, as is the rule during cardiac standstill after application of Stannius' first ligature, retrograde conduction is absent, it can be initiated by stimulating the auricles, thereby producing contractions in the normal sequence Once retrograde conduction is established in this way it persists so that successive ventricular stimuli are conducted to the auricles, but if stimulation is interrupted, retrograde conduction no longer takes place when stimulation of the ventricle is subsequently resumed The longer the standstill of the heart the more numerous the orthograde stimuli have to be in order to facilitate retrograde conduction. Similar conditions were observed on the junction between ventricle and bulbus (Skramlik, 1920a and b) These observations, which demonstrate facilitation* of retrograde conduction by stimuli passing in the normal direction, were discussed at some length since they also afford an understanding for the retrograde conduction of idioventricular impulses in cases of complete A-V block (*see* p 133) The reverse phenomenon, namely facilitation of orthograde conduction by retrograde stimulation of auricle from ventricle, when orthograde conduction had ceased, was found in the fish heart (Skramlik, 1927b).

The separation between conduction in the two directions is much less marked in the heart of the tortoise (Ishihama)

In the mammalian heart retrograde conduction to the auricles was reported by McWilliam in 1888 and by Bayliss and Starling in 1892 In the dog Stassen demonstrated reversed conduction from the ventricle to the auricle during vagus stimulation In most animals it was found to take place less readily than the orthograde one, the V-A intervals exceeding the A-V ones of normal conduction, but that reverse conduction over a certain distance, at least as far as the A-V node, is the rule is now generally accepted (Scherf and Shookhoff). If retrograde conduction is produced in the dog, alternation of the ventriculo-auricular conduction times is not uncommon (*see* Fig 80)

The importance of facilitation is illustrated by the observation that, if a ventricular rhythm is produced in dogs by means of induction shocks, the auricles respond to the ventricular beats only after a variable number of cycles (from three to twenty-seven, usually from five to twelve) (Lewis and Oppenheimer) Hukuhara and Komita, on the other hand, failed to find retrograde (V-A) conduction of ventricular extrasystoles in the dog.

S-A node, at a moment when they are already being activated by the next sino-auricular impulse and therefore are in their refractory stage. This is due to several factors, the most important ones being the heart rate, the delay of conduction in the A-V node (Hering; Lewis, 1921) and the length of the refractory period of the auricles.

* For definition of this term see p. 136

Clinical Observations

Since mechanical records alone do not allow a differentiation between ventricular extrasystoles with retrograde conduction to the auricles and A-V extrasystoles, the earlier reports of cases of the former arrhythmia, published before the advent of electrocardiography (Pan, Volhard, Gallavardin), cannot unreservedly be accepted The same holds good for the case published by Tancré, though it is often quoted, as the reproduced tracings are inadequate

The first convincing clinical example of ventricular extrasystoles with retrograde conduction to the auricles is the case published by Hart in 1912, in which an abnormally shaped P wave on the downstroke of the initial deflections of ventricular extrasystoles indicated retrograde conduction This interpretation was supported by the observation that, if such extrasystoles occurred in groups, only alternate extrasystoles showed the above sign of retrograde conduction A similar instance seems to be Case 4 in the series of Robinson and Herrmann (1921), though the authors do not mention retrograde conduction. Other cases, in which the presence of this arrhythmia in man seems established, are those of: Scott (1922) (electrocardiogram and venous pulse tracings), Gussenbauer (1923), whose case is particularly convincing since in the same record interpolated extrasystoles of the same shape without retrograde conduction were available for comparison, the post-extrasystolic intervals were compensatory, so that it has to be assumed that the retrograde impulses did not reach the sino-auricular node; Potts and Ashman (1926), in a case of dextrocardia; Allan (1926), in a case of ventricular paroxysmal tachycardia with retrograde conduction of every second beat, also showing the importance of facilitation, Samet, in whose case the post-ext
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was conducted as far as the sino-auricular node. Similar conditions are shown in a tracing of Lewis (1925), though Lewis concedes an alternative explanation of this record. Dressler, on the ground of his observations in two cases, emphasized the importance of facilitation of conduction for the establishment of retrograde conduction In his first case the presence of retrograde conduction of ventricular extrasystoles could be demonstrated particularly clearly, since the underlying rhythm at times was dissociation with interference (*see* p 178), at other times A-V rhythm with preceding activation of the ventricles, and the inverted P′ waves following the initial deflections of the ventricular extrasystoles had the same shape in the electrocardiogram as the P waves during A-V rhythm. During the periods of fully developed A-V rhythm, retrograde conduction of ventricular extrasystoles occurred almost without exception, this observation illustrating the importance of facilitation. Occasionally, however, ventricular extrasystoles were conducted to the auricles when the underlying rhythm was dissociation with interference. Since, in this arrhythmia, a block of the conduction of A-V impulses to the auricles has to be postulated (*see* p 179), the retrograde conduction of ventricular extrasystoles to the auricles is difficult to understand. As, in this case, the transition from A-V rhythm to dissociation with interference was associated with a conspicuous slowing of both the independent auricular and ventricular rhythms, considered to be due to a vagal effect, Dressler explains the retrograde conduction of ventricular extrasystoles during dissociation with interference by the assumption that the increase in vagal tone resulted in a diminution of strength of the A-V impulses which, for this reason, were no longer conducted to the auricles, whereas the strength of the impulses of the ventricular extrasystoles was less, if at all, diminished.

Ventricular extrasystoles with retrograde conduction, in which the impulse reached the sinus node, were also described by Meyer

In order for a diagnosis of retrograde conduction of ventricular extrasystoles to the

auricles to be made from the standard leads, it is necessary that in the electrocardiogram a P wave, which is low positive or isoelectric in lead 1 and sharply inverted in leads 2 and 3, follows an abnormal QRS complex, itself not preceded by a P wave, with a R-P segment equal to or exceeding the P-R interval of the individual case, the whole of such P waves, usually designated P′, has to be below the line otherwise occupied by the S-T segment Caution is necessary not to confuse with such P′ waves normal P waves occasionally visible in the final deflection of the extrasystole. The post-extrasystolic intervals may be shorter than compensatory or compensatory, according to whether or not the retrograde impulse reached the sino-auricular node The diagnosis of this arrhythmia is rendered more certain if only some of the extrasystoles are conducted in the reverse direction, so that the shape in the electrocardiogram of undistorted extrasystoles is available for comparison, and if the post-extrasystolic interval is not compensatory Even so, the differentiation from A-V extrasystoles with preceding activation of, and aberrant conduction in, the ventricles may be difficult, if not impossible In the latter arrhythmia there would be the same shape, and position in relation to the QRS complexes, of the P waves as well as abnormally shaped ventricular deflections, but since ventricular extrasystoles tend to have the same shape in the electrocardiogram, whereas with aberrant conduction in the ventricles of supraventricular impulses the degree of aberration tends to vary from beat to beat, identical forms of the abnormally shaped ventricular complexes would favour the diagnosis of ventricular extrasystoles with retrograde conduction

The value of oesophageal leads for the detection of retrograde P′ waves in this arrhythmia was emphasized by Brown

Quite recently Kistin and Landowne published an important paper in which, employing oesophageal leads, they reported evidence of retrograde conduction of ventricular premature beats in fifteen out of thirty-three unselected subjects These authors found (unipolar) oesophageal leads from atrial levels (37·5 cm) particularly informative The characteristics of the P′ waves, interpreted as indicating retrograde conduction, are listed as follows· (1) they may differ in shape from the sinus P waves, (2) they may be premature in relation to the sequence of the sinus P waves and, in such event, the P′-P interval—that is, the interval between the retrograde P′ and the following sinus P wave—is longer than the P-P one, and the interval between the last P wave before, and the first P wave after the extrasystole may be compensatory or shorter than compensatory; (3) such P′ waves occur only within a limited range of time after the preceding extrasystolic QRS complex A further reliable criterion of retrograde conduction were fusion P waves, intermediate in shape between P′ and P waves These authors demonstrated, in our opinion conclusively, that such oesophageal leads did indicate retrograde conduction in a considerable proportion of cases in which the simultaneously recorded lead 2 failed to do so. They put forward good reasons to explain this, based on the effect, upon the P waves in the oesophageal lead and lead 2 respectively, of two such excitation waves travelling between the S-A and A-V nodes in opposite directions These authors also point out that, in quite a number of instances, a " compensatory " post-extrasystolic interval may be a fortuitous occurrence, caused by the unavoidable inclusion, in the measurement of this interval, of variations in the sinus rate and margins of error of measurements On the other hand, post-extrasystolic intervals after ventricular extrasystoles with retrograde conduction tend to be truly " compensatory ", since the retrograde impulse is likely to reach the sinus node only after the initiation of the next S-A impulse This follows from the fact that such retrograde conduction takes place with less prematurity than does the occurrence of some auricular extrasystoles the post-extrasystolic intervals of which tend to be shorter than compensatory Other noteworthy findings of these authors were that the ventriculo-auricular conduction time in the human heart is not consistently greater than the orthograde atrio-ventricular one, and that in two of their cases the intervals of retrograde activation fell into two discontinuous groups, which

is interpreted as denoting two pathways of retrograde conduction. (An analogous assumption regarding a double pathway of auricular activation in certain instances of return extrasystoles was made by Decherd and Ruskin, *see* p 118.) In one of these authors' cases, an otherwise healthy subject with short runs of ventricular tachycardia, the first ectopic beat of such series did not show evidence of retrograde conduction whereas this occurred in the remaining beats of such series. This is the clinical counterpart of Lewis' and Oppenheimer's experimental observations, discussed earlier in this section, and illustrates the importance of facilitation

In our opinion the tracings published by Kistin and Landowne are convincing and these findings may necessitate a reconsideration of our views about the incidence of retrograde conduction of ventricular extrasystoles in the human heart. In view of the great physiological importance of the points raised by this publication we should like to reserve our final judgment until these findings are confirmed and corroborated by other leads, further information could be expected, for instance, from unipolar limb or certain intracavity leads

A few personal observations may now be described.

Fig 89 provides an example which also demonstrates the value of the chest leads It was obtained from a seventy-year-old patient with syphilitic aortitis, atheromatosis and angina of effort One ventricular extrasystole is reproduced in leads 1 and 3 respectively which at first glance give the impression of being of the usual variety. Closer inspection and measurement show, however, that the post-extrasystolic intervals are far shorter than compensatory, that no P wave is visible at the expected time after the extrasystole and that a small wave was inscribed in the descending limb of the T wave of the extrasystole in lead 1 and the ascending limb of the S wave in lead 3, the interval between such waves and the following P waves equalling the normal P-P intervals. This suggests ventricular extrasystoles with retrograde conduction and this assumption is made more probable by the features of lead CR-3, in which three ventricular extrasystoles were recorded, the first two of which show well-defined inverted P′ waves on the ascending limb of the S waves, the R-P′ intervals being 0 15 and 0 16 second as compared with the 0 15 second of the P-R intervals of the sinus beats The R-R intervals being 1 09–1·13 seconds and the coupling of the first two extrasystoles being 0 45 second, the post-extrasystolic intervals of 1·44 and 1·40 seconds respectively fall far short of being compensatory, and the P′-P intervals equal the P-P ones The third extrasystole occurred with a longer coupling, 0·52 second No P′ wave is visible on the ascending limb of its S wave, and while it is therefore not possible to determine the R-P′ interval, the steeper ascent of the S wave and the greater height of the T wave as well as measurement backwards from the following P wave make it possible to state that its R-P′ interval was shorter than the one of the two preceding extrasystoles. This would have to be expected in view of the longer coupling. The post-extrasystolic cycle was terminated by an escape beat. These observations point to an interpretation of ventricular extrasystoles with retrograde conduction, and the constancy of the shape in the electrocardiogram of the extrasystoles supports this view and allows to exclude the only other alternative, namely, A-V extrasystoles with aberrant ventricular conduction. The tracing also shows an interesting alteration in the shape of the P wave of the post-extrasystolic beats following the second and third extrasystole, such waves being more peaked than the other P waves This is reminiscent of similar conditions after auricular extrasystoles, indicating that impulse formation continues in another auricular centre. That such ectopic auricular impulse formation may continue for several beats after an auricular extrasystole was shown in Fig 46 Strong support of the presence of retrograde conduction is afforded by lead CR-4, in which the P′ wave is particularly distinct, the P′-P interval equalling the P-P one: this portion of the record could hardly be interpreted in any other way.

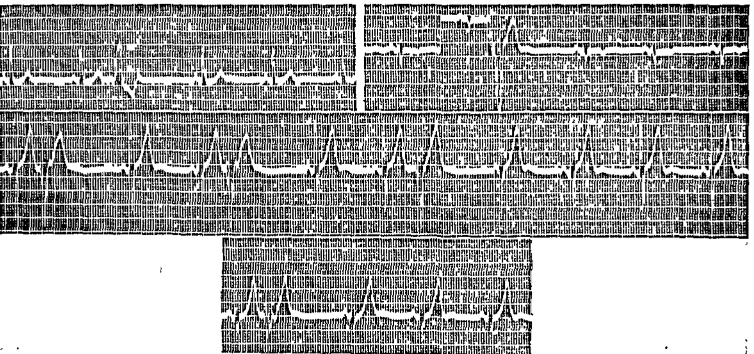


FIG 89—Leads 1, 3, CR-3 and CR-4 Retrograde conduction of ventricular extrasystoles. For further explanation, see text

Fig 90a was obtained from a sixty-five-year-old patient with coronary sclerosis The tracing shows two sinus beats followed by a ventricular extrasystole, in the final deflection of which an inverted wave is visible which has all the appearances of an inverted P (P′) wave The R-P′ interval measures 0 20 second as compared with the 0·13 second of the P-R intervals of the sinus beats The post-extrasystolic interval was fully compensatory, but since the P′ wave indicating retrograde conduction occurred at a time when the next normal P wave was due, this record is best interpreted as showing a ventricular extrasystole with retrograde conduction reaching the auricles at the moment when the next normal impulse is being formed.

Fig 90b, obtained from a healthy man of forty-six, shows similar conditions After a sinus beat a ventricular extrasystole was recorded, in the final deflection of which a P′ wave is visible, occurring after a R-P′ interval of 0·20 second at a time when the next

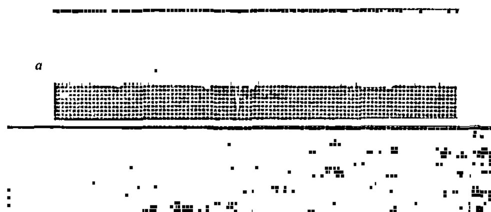


Fig 90 —Both tracings lead 2, obtained from different patients Retrograde conduction of ventricular extrasystoles

normal P wave was due. The P-R intervals of the sinus beats measured 0 18 second The post-extrasystolic interval was more than compensatory and the P′-P interval (1·12 seconds) was longer than the normal P-P ones (0 96–1·00 second) These time relations seem best explained by the assumption that the retrograde impulse reached the sinoauricular node, there causing an inhibition of the formation of the subsequent impulse; this phenomenon would be analogous to the one discussed in relation with the post-extrasystolic intervals following auricular extrasystoles (*see* p. 47) A case similar in many respects was published by Holzmann

Regarding retrograde conduction of ectopic beats in parasystole, see chapter on "Pararrhythmias", p. 156

SUMMARY

Retrograde conduction of ventricular extrasystoles is common in certain animals, but its occurrence in man has until quite recently been considered very rare. In order for a diagnosis of this arrhythmia to be made from the standard leads it is necessary that in the electrocardiogram a P wave, which is low positive or isoelectric in lead 1 and inverted in leads 2 and 3, follows an abnormal QRS complex, itself not preceded by a P wave, with an R-P interval equal to or exceeding the P-R interval of the individual case; in leads 2 and 3

the whole of such P waves has to be below the line otherwise occupied by the S-T segment. The post-extrasystolic interval may be shorter than compensatory or compensatory, according to whether or not the retrograde impulse reached the sino-auricular node The differentiation from A-V extrasystoles with preceding activation of, and aberrant conduction in, the ventricles may be difficult, if not impossible, identical forms of the abnormally shaped ventricular complexes favour the diagnosis of ventricular extrasystoles with retrograde conduction. Mechanical records do not make a differential diagnosis between these two arrhythmias possible and cases published before the advent of electrocardiography as indicating retrograde conduction of ventricular extrasystoles cannot unreservedly be accepted, particularly since the alternative arrhythmia, namely, A-V extrasystoles cannot be differentiated from such records A brief review of the published cases is given, to which a description of three personal cases is added The importance of facilitation of conduction for establishing retrograde conduction is emphasized

If a recent observation, based on oesophageal leads, of the common occurrence of retrograde conduction of ventricular extrasystoles in the human heart is confirmed on larger series of cases, our views about the incidence of this phenomenon will have to be reconsidered (For references see next section)

RETROGRADE V-A CONDUCTION OF VENTRICULAR AUTOMATIC BEATS AND OF VENTRICULAR EXTRASYSTOLES IN COMPLETE A-V BLOCK

If, as discussed in the preceding section, the retrograde conduction of ventricular extrasystoles was until recently believed to be a rare event in cases of sino-auricular rhythm, that of automatic ventricular beats and of ventricular extrasystoles in complete A-V block was for a long time considered to be an impossibility That in the absence of conduction in the normal direction retrograde conduction should occur at all seemed so unlikely that all kinds of other explanations were put forward when clinical cases first came under observation in which this occurrence was seemingly present Yet, in our opinion this phenomenon is not at all uncommon

Cohn and Fraser who were the first to report in 1914 a case of complete A-V block, in which some of the ventricular beats seemed to activate the auricles, attributed the premature auricular contractions to a mechanical stimulation of the auricles by the contracting ventricles, the long refractory period of the auricles playing an important part. Barker thought that the abnormal impulse responsible for auricular contraction, being due to mechanical stimulation by the ventricles, originated above the lesion in or near the A-V node, whence it was conducted to the auricles, he specifically rejected the assumption of retrograde conduction Similar views were expressed by Wilson and Robinson

The first to suggest retrograde conduction of automatic beats in a case of complete A-V block were Danielopolu and Danulescu (1922) Similar cases were reported (Veil and Codina-Altès, Wolferth and McMillan, Froment *et al*, Bain, Kisch and Zucker a o) and by 1944, twenty-five cases showing this phenomenon were collected in a critical review by Winternitz and Langendorf, including six new cases More recent observations are contained in the papers by Duclos (one case), by Segers (three cases; in Case 3, retrograde impulse precipitated a more rapid ectopic auricular rhythm with the same inverted P′ waves, terminated by an idioventricular beat which was also reversedly conducted), and by Gallavardin, Froment and Balestier Their observation, made in a forty-eight-year-old woman with rheumatic mitral valvular disease and complete A-V block, showed that retrograde conduction took place only with idioventricular beats which had a P-R interval varying between 0 43 and 0 52 second, whereas with some beats occurring with a P-R interval exceeding 0·52 second no retrograde conduction occurred. This observation is interpreted

as probably indicating a supernormal phase of retrograde conduction. Carotid sinus sure slowed the auricular rhythm, the P-P intervals lengthening from 0·62 to 0 80 se and resulted in a conspicuous increase in the number of beats with retrograde condu Atropine, on the other hand (1 mgm., given intravenously), accelerated the auri rhythm and abolished retrograde conduction.

While the reader is referred to the exhaustive paper of Winternitz and Langen which includes a complete list of such cases up to 1944, and a well-reasoned rejection explanations other than retrograde conduction of automatic ventricular beats, we pr to add a short description of two observations of our own and to discuss briefly some p which we consider to be of especial interest

Fig 91 was obtained from a seventy-four-year-old man with hypertension and corc sclerosis The record shows complete A-V block (auricular rate about 65, ventricula Inverted P waves (P′) are seen after the third ventricular complex in lead 2 and afte first and fifth ones in lead 3, the R-P′ interval being 0 18 second

This case shows some features which were observed in most of the records publish far the P′ waves indicative of retrograde conduction were inverted in leads 2 an evidence of retrograde conduction occurred only when an automatic beat fell comparat late in auricular diastole (the P-R intervals preceding the beat with retrograde condu being 0·6, 0 66 and 0·74 second respectively), the R-P′ intervals were well within the l of normal forward conduction time, the auricular rate was not fast, the record was tained from an old patient with evidence of structural heart disease

The P′ waves in any individual lead may vary somewhat in shape (*see* Fig. 91, lea this is due to the time of their occurrence within the R-T (S-T) interval and to interfer between the retrograde P′ with the orthograde P if this is due at about the same time. latter mechanism constitutes one of the varieties of summation beats. (For a recent ger review of such beats (also called fusion beats), *see* Malinow and Langendorf)

Fig 92 reproduces an unusual record, obtained from a sixty-five-year-old wo suffering from anginal pain, dizziness and attacks of fainting The tracing shows com A-V block The first, third and fourth automatic idioventricular beats and the ventric extrasystole are reversedly conducted to the auricles the initial ventricular deflection these beats are followed by the characteristic sharply inverted P′ waves.

The fact that retrograde transmission in the absence of conduction in the normal di tion has to be accepted should be stressed since as late as 1931 its occurrence was dou (Zeisler) Conclusive proof is contained in the paper by Wolferth and McMillan showed that, if a ventricular extrasystole with retrograde conduction follows an autom beat with a fixed coupling, the R-P′ interval of the extrasystole is longer when the ceding automatic beat also was reversedly conducted Moreover, in all published rec retrograde conduction was only reported of beats occurring late in auricular diast Neither of these observations could be explained by the assumption of a mechanical sti lation of the auricles by the ventricles, nor would the time relations be compatible Barker's view of the precipitation of an auricular extrasystole by the automatic beat. I large proportion of the reported cases the block was unstable, but retrograde conduct was seen only when A-V block was complete; in the only case in which this occurrence reported during 2 : 1 block (Wolferth and McMillan, Case 2), in our opinion complete block actually was present, since there was considerable variation in the length of the intervals

Retrograde conduction in the absence of orthograde one is a manifestation of unidi tional block, the presence of which has to be postulated also in cases of dissociation interference (*see* p. 178), and return extrasystoles (*see* p 120) Such unidirectional bl was produced in strips of ventricular muscle of the tortoise by asymmetric mechanical c pression (Ashman and Hafkesbring, 1929). These authors showed that, if in this way a z

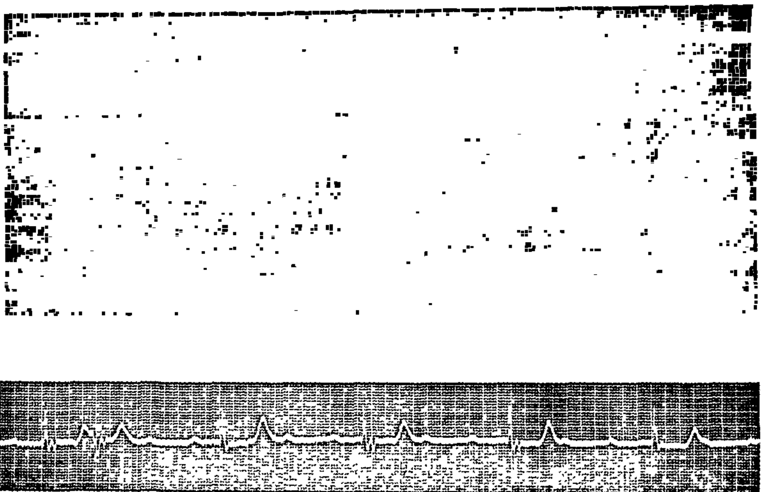


FIG 92 —Lead 3 Retrograde conduction of automatic idioventricular beats and of a ventricular extrasystole in a case of complete A-V block

of strongly compressed muscle is produced adjacent to one which is lightly compressed, a stimulus produced at one end of the strip, which first traverses the zone of strong compression, was conducted to the other uncompressed end of the strip, whereas a stimulus of equal strength precipitated at the opposite end and having to pass first through the lightly compressed area was blocked Moreover, before irreciprocal conduction is thus produced, the impulse will usually traverse the strip more rapidly in the direction from stronger to weaker compression than in the opposite one. The explanation put forward is that in the more strongly compressed area the impulse is conducted with a larger decrement (*see also* Drury); the remaining strength is adequate for the stimulus to pass through the zone of less resistance. With an impulse set up at the opposite end, the decrement it suffers while traversing the lightly compressed area weakens it to such an extent that it fails subsequently to pass the strongly compressed part. The same view had been put forward by Wolferth and McMillan, with this apposite simile. " The point may perhaps be made clearer by the analogy to a runner who might be able to jump a broad stream at the beginning of his race and then overcome relatively minor obstacles, whereas if the minor obstacles had come first he might have been so fatigued as to be unable to jump the broad stream."

Dissociation with interference has already been mentioned as another condition in which unidirectional block is a prerequisite As a section is devoted to this arrhythmia, this only need be said about it here, that in it a faster A-V rhythm and a slower S-A rhythm coexist and that the slower S-A rhythm at times interferes by conducted beats with the faster A-V rhythm Such a condition is only possible if the centre of the slower rhythm is protected from the faster impulses originating in the A-V node and this block can be effective only in the retrograde direction from the A-V node towards the S-A node, whereas the spread of the excitation wave in the normal direction is unimpaired. Retrograde conduction of automatic ventricular beats and of ventricular extrasystoles in complete A-V block is *therefore the reverse of dissociation with interference and, in accordance with Winternitz and* Langendorf, could be termed dissociation with interference between ventricle and auricle.

An attempt was made by Kline, Conn and Rosenbaum to explain retrograde conduction in complete A-V block by the " supernormal phase " of recovery According to Adrian and Keith Lucas, who first described this phenomenon, it can be defined as a temporary overswing of the recovery curve of excitable tissue after the transmission of an impulse, during this period stimuli of an intensity, which at any other time would be subliminal, will become effective. Its presence in cardiac muscle under definite experimental conditions was established by Adrian and several clinical cases have been reported (Scherf and Schott, for a recent critical review *see* Mack, Langendorf and Katz, also chapter on " Mechanism ", p 497) Its presence was made probable in Case 2 of Kline *et al.*, though the fact that in the short reproduced strip the P waves, considered to have been due to retrograde conduction, have the same shape in the oesophageal lead as the P waves of beats of sino-auricular origin raises doubts about the criteria applied by these authors to determine retrograde conduction. Even if the presence of a supernormal phase of recovery of conductivity is conceded as a possible explanation in this case, it is inapplicable to others (Winternitz and Langendorf, Case 2).

In the present state of our knowledge it seems to us preferable to consider facilitation of retrograde conduction by an orthograde impulse as the mechanism usually operative (*see also* Skramlik, p 127) This would account for the observation that, in the majority of such cases, retrograde conduction is observed only if the idioventricular beat showing this phenomenon occurs late in auricular diastole, at a time when the next sino-auricular impulse either has started or is about due. The term facilitation is used here as commonly employed, in neurophysiology, in the wider sense of the German " Bahnung " It means, in a general way, that because of some antecedent or concomitant event " the job is more easily done" or " a bigger job can be done" (Lloyd) While the supernormal phase is of great importance

in facilitation, thus defined, other factors are likely to be also responsible for it. This is more fully discussed in the chapter on "Mechanism", p. 497. The relevant physiological observations providing a basis for considering facilitation as the underlying mechanism for retrograde conduction were discussed in the preceding section.

According to Danielopolu and Danulescu the retrograde conduction of only those automatic beats which occur late in auricular diastole was due to the length of the refractory period of the auricles, the duration of which could thus become measurable. It was shown, however, by Winternitz and Langendorf that "it is the state of the junctional region of depression or block, and not of the auricle, which determines whether retrograde transmission will occur or fail". In one of their cases of complete block with occasional retrograde conduction, at times an ectopic auricular rhythm was present, characterized by inverted P waves (—P), at other times normal upright P waves were recorded (+P); (*see* Fig 93). Ventricular extrasystoles (P B, Fig. 93c) with retrograde conduction were also occasionally present. The authors found that the earliest retrograde conduction after an

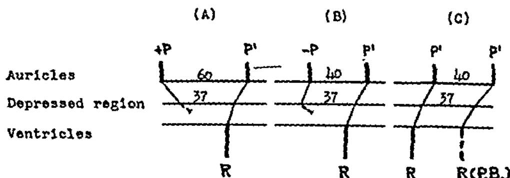


FIG 93—From WINTERNITZ and LANGENDORF, *Am Heart J*
For explanation, see text

upright P wave occurred with a much longer +P—P′ interval than the earliest retrograde conduction after an inverted P (—P—P′) Beats giving rise to a +P arise in or near the sino-auricular node, whereas those producing —P are due either to a retrograde transmission or to a supra-ventricular escape of a beat originating above the area of block. The authors point out that in the longer +P—P′ intervals the additional time required by the impulse from above to reach the depressed region and by the ventricular impulse to travel from the depressed region to the auricle is included These time relations can be explained by the assumption that they are determined by the state of the area of depression, but not by the length of the refractory period of the auricles

These observations have also a bearing on the question whether the retrograde transmission uses a path different from that of the orthograde one While the importance of accessory pathways is now definitely established in some instances (for example the Wolff-Parkinson-White syndrome), it seems probable that in the retrograde conduction of automatic ventricular beats and ventricular extrasystoles in complete A-V block the same

shows retrograde transmission than when it does not. A similar problem arises in connexion with return extrasystoles (*see* p 123).

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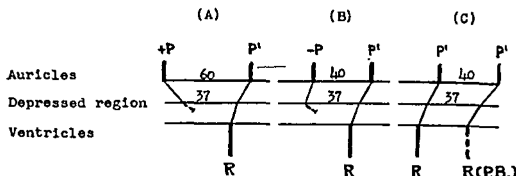


FIG 93—From WINTERNITZ and LANGENDORF, *Am Heart J*
For explanation, see text

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These observations have also a bearing on the question whether the retrograde transmission uses a path different from that of the orthograde one While the importance of accessory pathways is now definitely established in some instances (for example the Wolff-Parkinson-White syndrome), it seems probable that in the retrograde conduction of automatic ventricular beats and ventricular extrasystoles in complete A-V block the same pathways are used, at least for a distance This view is based on the findings of Winternitz and Langendorf, also on the findings of Wolferth and McMillan, mentioned earlier, that the R-P′ interval of a ventricular extrasystole is greater if the preceding automatic beat also *shows retrograde transmission than when it does not.* A *similar problem arises in* connexion with return extrasystoles (*see* p. 123)

As far as the scanty anatomical observations make it possible to express an opinion it seems that the site of the area of depressed conduction or block, rather than the presence of accessory pathways, is responsible for the retrograde transmission. In the three cases in which histological findings were reported (Wolferth and McMillan, Lequime and Sanabria, Winternitz and Langendorf) the degenerative changes were situated in the common bundle near its bifurcation and the upper portions of one or both main branches, whereas the A-V node and the upper part of the bundle of His were relatively unaffected. That this may be more than a coincidence is indicated by the observation that retrograde conduction of automatic ventricular beats has been reported in cases of complete A-V block with variable ventricular complexes (Bain)· It was pointed out on p. 100 that this seems to denote active foci in both main branches. The co-existence of these two rather rare phenomena would be consistent with, and perhaps point to the presence of, lesions in the region of and below the bifurcation Further observations are required to establish whether retrograde conduction in complete A-V block indicates this particular localization of the lesion

SUMMARY

The retrograde conduction to the auricles of automatic ventricular beats and ventricular extrasystoles in cases of complete A-V block must be considered as established This observation, implying the presence of retrograde conduction in the absence of conduction in the normal direction, was until comparatively recently considered so improbable that various other explanations had been put forward, all of which a critical review has shown to be untenable On the other hand, this seemingly unlikely occurrence becomes understandable, if it is related to the relevant physiological observations on unidirectional block and on facilitation of conduction by impulses passing in the opposite direction It is possible that retrograde conduction in complete A-V block indicates that the site of the lesion is in *the common bundle near its bifurcation and in the upper portions of both bundle branches*, but further observations are required to substantiate or refute this conclusion

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EXTRASYSTOLES IN GROUPS

Extrasystoles in groups is defined as an arrhythmia in which two or, rarely, more ectopic beats originating in the same centre follow one another at a shorter interval than that separating such groups from each other There is therefore an alternation in cycle length in this arrhythmia while the ectopic rhythm prevails, but the ventricular complexes have identical shapes

There are several reasons for the suggestion that this arrhythmia should be considered as a separate entity

Firstly, the historical aspect As two beats succeed one another at a comparatively short interval, this group being separated from the following one by a longer interval, this arrhythmia forms one variety of bigeminal, or coupled, rhythm In the chapter on coupling it is pointed out that, for a considerable time, great confusion prevailed about the kind of arrhythmia to which the term " bigeminy " should be applied While the reader is referred to that chapter it should here be recalled that, originally, Wenckebach wished to restrict the use of this term to that variety of bigeminal rhythm in which the two ectopic beats originated in the same ectopic focus, a contention which was abandoned when it became established that, in the great majority of instances, such rhythm is due to a sinus beat followed by an extrasystole. The arrhythmia, discussed in the present section, therefore constitutes what Wenckebach called " true bigeminy ". In view of the former confusion about the connotation of this term, however, it was considered inadvisable to revive this name and " extrasystoles in groups " was suggested instead (Scherf and Romano)

Secondly, this arrhythmia is one instance of repetitive impulse formation in one centre Repetitive response to various kinds of stimuli, in particular to continuous ones, has [illegible]

more frequently if records are examined more consistently for this disturbance.

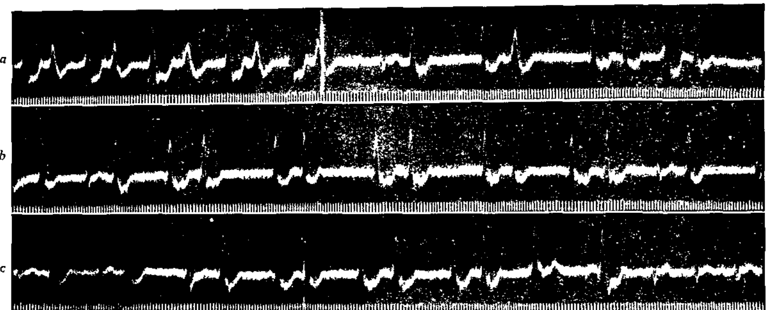


Fig 94 —All tracings lead 3 The record was obtained immediately after the intravenous injection of 0 4 gramme of quinine bihydrochloride Between the strips *a* and *b*, as well as between *b* and *c*, about twenty contractions are omitted *a* the beginning shows ventricular tachycardia with alternating shape of the QRS complexes The middle shows the abrupt ending of this tachycardia about thirty seconds after the injection, after one bigeminal group consisting, of a ventricular extrasystole coupled to a normal sinus beat, extrasystoles in groups occurred *b* and *c* Extrasystoles in groups followed by restoration of sinus rhythm (end of *c*) Time base 0 04 second From Scherf and Romano (*Amer Heart J*)

Experimentally, extrasystoles in groups were seen in instances of digitalis intoxication (Kobacker and Scherf; Scherf, 1927), during the topical application of barium chloride or strophanthin (Scherf and Romano), or after the intravenous injection of acetylcholine followed by atropine (Scherf, Chick *et al*) In man, this type of irregularity was found in respect of auricular as well as of ventricular ectopic beats (MacKinnon; Rachmilewitz and Scherf, Scherf and Romano)

Fig 94 provides an example It was recorded in a patient suffering from " Extrasystolie à paroxysmes tachycardiques " (*see* p 237) During the tachycardia alternation of the QRS complexes was observed After the intravenous injection of 0 4 gramme of quinine bihydrochloride typical " extrasystoles in groups " occurred until finally sinus rhythm was

ventricular extrasystoles Warming of the area to which strophosid had been applied resulted in an increase in the number of ectopic beats which occurred as extrasystoles in groups with alternation in the cycle lengths between successive beats The lengths of successive cycles measured 0·32, 0 34, 0 37, 0 31, 0 39, 0 31, 0 38, 0 32, 0 39 second, etc. In our opinion the last-mentioned observation strongly supports the view that these extrasystoles are due to repetitive impulse formation in a centre (see Chapter on " Mechanism ", p 503)

Alternation of cycle length also occurs often during auricular flutter elicited by faradiza- ... not see any difference in principle ... icular disorders of rhythm and the

Grouped discharges are also a well-known phenomenon in neurophysiology. For example, chemical stimulation of nerves of frogs (Brink, Bronk and Larrabee) and injury of mammalian nerves (Adrian) are known to produce this type of response. This is more fully discussed in the chapter on " Mechanism " (p 503)

SUMMARY

Extrasystoles in groups is defined as an arrhythmia in which two ectopic beats origin-

rhythm, experimental as well as clinical, are reviewed and illustrated by personal observations.

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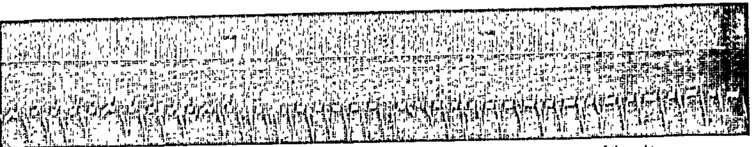
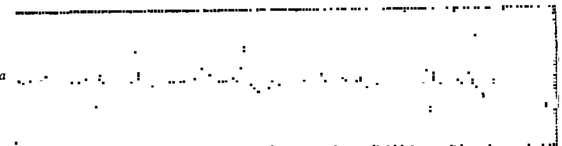


FIG 95 —From an experiment on a dog. After the sub-epicardial application of strophosid to the conus of the right ventricle an arrhythmia was recorded whereby one sinus beat was followed by four right-ventricular extrasystoles (beginning of the record). Warming of the area of application of strophosid resulted in extrasystoles in groups. Beginning and end of warming indicated by black lines. For further explanation, see text



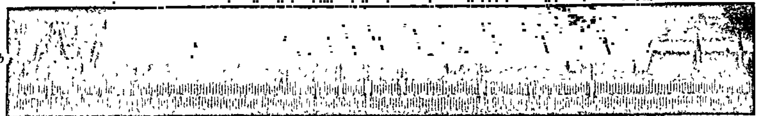


FIG 96 —*a* Lead 3. Four ventricular extrasystoles, each of a different shape. *b* Lead 3. Extrasystoles originating in two ventricular foci and occurring in series. At times the ectopic rhythm shows alternation

MULTIFORM EXTRASYSTOLES

A large proportion of extrasystoles, auricular as well as ventricular, show a remarl constancy of form over long periods, sometimes amounting to many years As alı referred to, they are found in otherwise healthy subjects, and their presence certainly not signify myocardial disease though it does not exclude it. The inference is that the ginate in the same focus, which is likely to be small and which at an early stage of ele cardiography was thought to be situated in the specific tissue (Lewis and Silberberg) easily understood that such a small focus of presumably only one or a few abnorı irritable cells is well compatible with an otherwise healthy myocardium (*see also* ch on " Mechanism ")

If, on the other hand, extrasystoles of varying shapes are encountered, the presen several abnormal foci, or of associated intra-ventricular disturbances of conductio both has to be postulated. From this it may be inferred that such multiform extrasys are more likely to occur in patients with more extensive myocardial changes. Cl experience in fact shows that they indicate myocardial disease. Thus, this variety of e systoles is frequently found in coronary sclerosis, diphtheria with myocardial necros myocarditis—to quote a few instances.

Digitalis may lead to the occurrence of multiform extrasystoles, but only in patients myocardial disease (*see* section on " Digitalis ")

As such extrasystoles of varying shape have to be assumed to arise in several foci are also called multifocal by some authors We prefer the term multiform (or varyforr polymorphous), since the presence or degree of associated disturbances of intra-ventri conduction cannot be separated from the varying site of origin, as far as the electroca graphic appearances are concerned. Mahaim (1931, p 425) pointed out that this "polymorphe" (multiform) should refer only to ventricular extrasystoles of varying form, should not be employed for instances in which a combination of extrasystoles originati different portions of the heart are found in the same patient (for instance auricles and node); for the latter variety he suggested the term polytopic While we concur with view of Mahaim, we will also use " multiform " for auricular extrasystoles with var shapes of the P waves. Clinically, multiform (or varyform) extrasystoles of ventri origin are much the more important

The diagnostic importance of multiform *ventricular* extrasystoles has been stresse various authors. D'Irsay, in a series of a hundred patients with ventricular extrasys (66 uniform, 34 multiform), found that the percentage of pathological changes in the r cardium was considerably greater in patients with multiform than in those with unif premature beats Whereas diseases not involving the myocardium were not accompa by varyform, though sometimes by uniform extrasystoles, multiform ones were al associated with myocardial disease. Similar views regarding the diagnostic and progn significance of multiform extrasystoles were held by others (Peel; Avezzù and Cł Such extrasystoles of various shapes sometimes occur in series and were thus c " anarchie ventriculaire " (Clerc and Lévy; Mahaim, 1928, 1931). Their unfavour prognostic significance is exemplified by the epithet " terminal" (Gallavardin, Dieu and Davidson)

Figs 96 and 97 provide examples. Fig 96a, obtained from a patient of sixty-four coronary sclerosis and angina pectoris who had not received digitalis, shows four ventric extrasystoles, each of a different shape. Fig 96b, recorded from a patient with coro sclerosis sixteen days before death (no digitalis treatment) shows ventricular extrasys occurring in series and originating in two foci; at times there was alternation in the sl of such ectopic beats There was marked arrhythmia of the ectopic rhythm, even if suc sive beats arose from the same site.

Fig. 97, obtained from a man of sixty-seven with congestive heart failure due to coronary sclerosis a few days before death, shows multiform ventricular and also auricular extrasystoles. There was no digitalis treatment

Sudden death is not uncommon in patients with multiform ventricular extrasystoles, due, presumably, to ventricular fibrillation



Fig 97—The three standard leads and lead CR-4 Auricular and multiform ventricular extrasystoles

Varyform ventricular extrasystoles are particularly common in association with pronounced disturbances of intra-ventricular conduction, that is, in complete A-V and in bundle branch block. Experimentally, they were recorded in experiments in which both bundle branches were severed or damaged (Wilson and Herrmann, 1921) Clinically, lesions of bundle branches were found histologically in cases in which multiform ventricular



Fig. 98.—Multiform ventricular extrasystoles in series in a patient with complete A-V block

Fig. 99.—[illegible] lead I, [illegible] lead CR-4. Multiform ventricular extrasystoles in series in a patient with complete A-V block.

extrasystoles had been associated with bundle branch block records (Mahaim, 1931). They were also observed in patients with complete A-V block, as illustrated by Figs 98 and 99 (*see also* Scherf)

Fig 98 was obtained from a patient with complete A-V block due to coronary sclerosis Every automatic beat was followed by a series of two to ten ventricular extrasystoles showing continually changing forms.

Fig 99 was recorded in a woman of sixty-two with complete A-V block, Adams-Stokes attacks and pronounced albuminuria. In the top tracing, the first automatic beat is followed by five ventricular extrasystoles with continually changing shapes, in the bottom tracing, the pronounced differences in the bizarre shape of the several ectopic beats are illustrated. Digitalis had not been given The patient died two days after the record was taken

The prognosis in patients with complete A-V block and multiform extrasystoles is grave; death due to ventricular fibrillation may supervene at any moment It seems reasonable to assume that the same lesion which produced the A-V block is also the cause of the multiform ectopic beats The giving of quinidine is dangerous in patients with complete A-V block since it may precipitate extrasystoles and ventricular fibrillation (*see* section on " Quinine ", p 290)

Every transitional stage between multiform extrasystoles, multiform ventricular tachycardia and ventricular fibrillation can be observed so that Gallavardin's term " préfibrillatoire " for such ectopic ventricular arrhythmias seems most apt (*see* Mahaim, 1931, p 424)

Denolin reported an interesting observation, made in a man of sixty with complete A-V block, in whom attacks of paroxysmal ventricular tachycardia with varying shape of the ectopic ventricular beats could be precipitated by exercise. His paper, to which the reader is referred, contains references to several further published instances of paroxysmal ventricular tachycardia in patients with complete A-V block

Ventricular tachycardia is one mechanism which may produce Stokes-Adams attacks in patients with complete A-V block, this occurrence is commoner than formerly assumed The same pathological lesion may thus produce A-V block, ventricular tachycardia and Stokes-Adams attacks

Multiform *auricular* extrasystoles are illustrated in Fig 100, which shows four records obtained from three different patients They reproduce auricular extrasystoles and shifting pacemaker, with continual change in the shape of the P waves. This type of auricular extrasystolic arrhythmia is often the precursor of auricular fibrillation (Langeron), an experience which we could often confirm.

SUMMARY

Whereas the common variety of auricular and ventricular extrasystoles with constant shape of the ectopic beats does not denote myocardial disease, extrasystoles with varying shape in the electrocardiogram are practically always associated with myocardial disease Their occurrence is favoured by concomitant digitalis treatment This variety of extrasystoles is termed multiform, or varyform, or polymorphous extrasystoles. The ventricular variety carries a serious prognosis which is even more grave if this arrhythmia is associated with more pronounced disturbances of intra-ventricular conduction (bundle branch block, complete A-V block) The auricular variety is often the precursor of auricular fibrillation

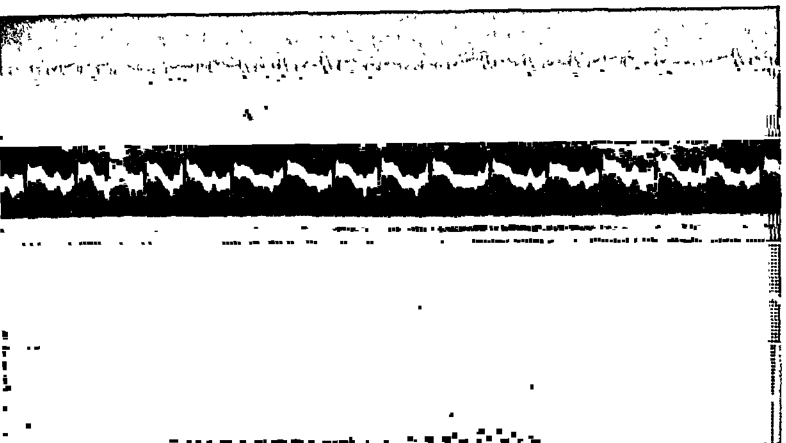


FIG 100.—All records lead 3, obtained from three different patients. Auricular extrasystoles with shifting pacemaker and continual change in the shape of the P waves multiform auricular extrasystoles

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Fig. 105, top tracing, shows an instance of parasystole with simple interference in which two successive ectopic beats occur at two places, the ectopic cycle length, thus directly measurable, was 1·12 and 1·09 seconds, (rate 53 and 55 per minute), that of the sinus beats 0·84–0·86 second (rate 70–71 per minute)

Parasystole with simple interference, while uncommon, is perhaps not quite as rare as the small number of published cases would indicate, and might be found more often if longer records were taken and analysed from this point of view. It has been estimated that its incidence is about 1 in 1,200 electrocardiograms in a general hospital In 1932 only eleven cases could be collected by Faltitschek and Scherf, including five of their own. In the attached table particulars are given of the forty-nine cases of which we are aware, including eighteen hitherto unpublished instances, in which we believe the diagnosis to have been established Only those cases were included in which the diagnosis of parasystole could be made with certainty It will be seen that this arrhythmia was somewhat more frequent in men than in women, amongst the forty-seven cases, in which the sex incidence is reported, were thirty-one men

TABLE 2 VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE.

No	Author	Age	Sex	Cardiac Condition	Rate S-A	Rate Ectop
1	SINGER AND WINTERBERG (1920)	20	m	Enlargement left ventricle	71	60
2	WINTERBERG (1923)	52	m	Aortitis	92–120	42–46
3	WINTERBERG (1923)	56	f	Arteriosclerosis and Hypertension	92–95	55
4	SCHELLONG (1924)	37	m	Nephritis one year previously, circulatory system normal	53–64	34–35
5	ZANDER (1927a)	40	f	Mitral incompetence	92	41–42
6	SCHERF AND SCHOTT (1930)	63	m	Coronary sclerosis	63–96	53–55
7	FALTITSCHEK AND SCHERF (1932)	30	f	Mitral and aortic valv. dis	109–117	89
8	„ „	56	m	Coronary sclerosis	130	83
9	„ „	63	m	„ „	81–92	61; 53
10	„ „	47	m	„ „	88	60
11	„ „	33	f	Mitral valvular disease	92	48–49
12	HOLZMANN (1934)	61	m	Advanced congestive heart failure	64–67	60
13	„ „	61	f	„ „ „ Hypertension, bigeminy	90	46
14	„ „	76	f	Advanced congestive heart failure, aur fibrillation	—	58–60
15	ECKEY (1936)	70	m	Advanced congestive heart failure	66	70
16	HILL AND CAMERON (1936)	59	m	One month after coronary thrombosis	56–60	42–46
17	ECKEY (1937)	38	f	Normal	55–69	40–45
18	„ „	25	m	„ (? familial)	83	35
19	„ „	54	m	After influenza, mild diabetes	62–68	51–52
20	VEDOYA AND BATTINI (1939)	12	f	Normal	109–133	133–139
21	ECKEY (1939)	24	m	After septicaemia Otherwise heart normal	68–80	34–35
22	„ „	18	m	Not stated	67–78	46
23	VEDOYA (1944)	50	m	Arteriosclerosis	69–87	54–55
24	„ „	48	m	Normal	74–87	38–40
25	„ „	51	m	Hypertension	73–100	33–39
26	HOLZMANN (1945)	72	f	Coronary sclerosis, cong heart failure	71–76	42–46
27	VEDOYA (1946)	45	m	Right bundle branch block Syphilis	91–109	32–34
28	VEDOYA, DUMAS AND URDAPILLETA (1948)	23	f	After acute gastro-enteritis	51–57	38–39

VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE—*Cont*

No	Author	Age	Sex	Cardiac Condition	Rate S-A	Rate Ectop
29	VEDOYA, DUMAS AND URDAPILLETA (1948)	37	f	Normal, but seven months after confinement, toxaemia of pregnancy	ca85	50
30	GENTILE (1950)	43	m	Normal, but one month after pneumonia	ca60	35–38
31	GALLAVARDIN AND FROMENT (1950)	45	f	Rheumatic mitral valvular disease	60–80	61–63
32	SCHERF AND SCHOTT	68	f	Carc recti	71	50
33	" "	56	m	Coronary sclerosis	78	45
34	" "	53	m	Hypertension	82	50
35	" "	34	f	Mitral stenosis, auric fibrillation	65*	50
36	" "	?	?	Coronary sclerosis, auric fibrillation	82*	41
37	" "	52	m	Hypertension	98	61
38	" "	71	m	Coronary sclerosis	70	44
39	" "	48	m	Hypertension	74	32
40	" "	?	?	Hypertension	84	41
41	" "	69	m	Coronary sclerosis	62	32
42	" "	68	m	" "	71	36
43	" "	70	m	Atheromatosis	75	28
44	" "	74	f	Myocardial infarction	84	31
45	" "	69	m	Hypertension	66	28
46	" "	53	m	Coronary thrombosis	85	34
47	" "	66	m	Coronary sclerosis	68	31
48	" "	66	m	Alcoholic cirrhosis, coronary sclerosis	70	21
49	" "	56	m	Coronary sclerosis	96	50

* Average ventricular rate.

The ectopic rate tends to be slow, but may vary between twenty-one and eighty-nine, (disregarding Vedoya and Battini's case which shows exceptionally high S-A and ectopic rates). Some relationship seems to exist between the rates of the two centres the slow ectopic rhythm of 34 was found in a patient with a sinus rate of 53–64, whereas the fast ectopic rhythm with a rate of 89 occurred in a case in which the sinus rate was 109–117. A similar relationship between the rates of the underlying A-V rhythm and that of an artificially produced ectopic rhythm was also seen experimentally (Scherf, 1926, Scherf and Chick), but clinically, as the table shows, does not hold good for all cases

Changes in rate of the sinus rhythm may be associated with changes in the same direction of the ectopic rate (Scherf and Boyd, 1950)

Diagnosis

The main diagnostic criteria have already been outlined above in this section (p 153), and the varying coupling of the ectopic beats and the simple mathematical relations between the inter-ectopic intervals were stressed as the most important features of this arrhythmia If the ectopic cycle length is directly measurable and a parasystolic mechanism is to be diagnosed, the inter-ectopic intervals must be multiples of the ectopic cycle length It was also emphasized that only those cases can be considered to be parasystole with simple interference in which—in addition to the above criteria—it can be shown that all impulses of both the sinus and the ectopic centre, which fall outside the refractory period of the preceding beat, yield responses. All these points require some qualifications and amplifications which are also of physiological interest.

Coupling. If the ectopic rate is slower than the sinus rate—and this is a prerequisite for

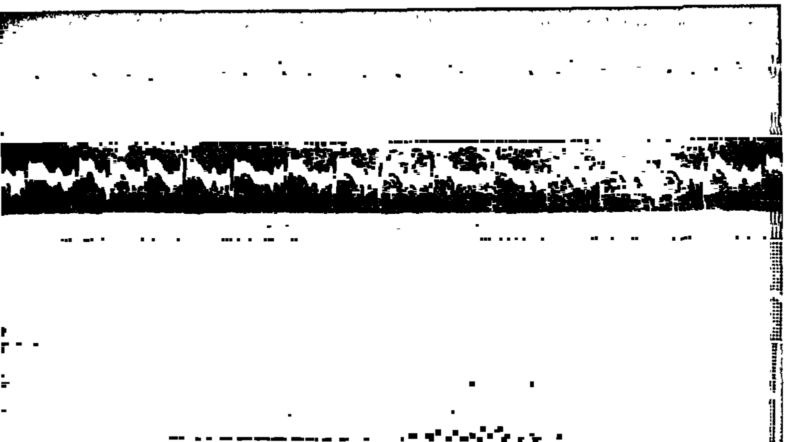


Fig 100—All records lead 3, obtained from three different patients. Auricular extrasystoles with shifting pacemaker and continual change in the shape of the P waves: multiform auricular extrasystoles

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CHAPTER III

PARARRHYTHMIAS

INTRODUCTORY REMARKS

Pararrhythmias represent a group of arrhythmias in which two (or rarely more) centres concurrently and independently produce impulses which yield contractions of the whole heart or parts of the heart, without disturbances of conduction of the normal [illegible] [illegible]g responsible for the arrhythmia It follows from this definition th[illegible] [illegible]e of the presence of two independent rhythms, [illegible] [illegible]ll within the category of pararrhyth[illegible]

At first sigh[illegible] as defin[illegible] [illegible] the centre o[illegible] [illegible] of the whole heart. In the no[illegible] [illegible] although all parts of the specialized conducti[illegible] [illegible] of impulse formation, though at lower rates, the sino-auricular [illegible]stroy all immature impulses in the other parts of the conducting system. In certain circumstances, however, these normal relations may be altered in such a way that two or more centres independently produce effective stimuli.

Two main groups of pararrhythmias may be distinguished· An automatic centre situated, with rare exceptions, in a ventricle may produce impulses interfering with those of the normal pacemaker, producing an arrhythmia termed parasystole, or a faster atrio-ventricular rhythm may co-exist with a slower sino-auricular rhythm, the resulting arrhythmia being termed dissociation with interference.

PARASYSTOLE

The idea that certain arrhythmias may be due to the rhythmic activity of two independent centres of impulse formation was put forward at an early stage of research on disturbances of cardiac rhythm. Thus Wenckebach (1903) used the term pararrhythmia for certain extrasystolic arrhythmias with persistence of the basic cardiac rhythm and ascribed certain " dissociations and interferences of rhythm " to the activity of two independent auricular centres (Wenckebach, 1906, Case V, same case, 1914, IV, 3, p. 100) or postulated two functionally dissociated parts of the venous musculature (1907, Case VIII, p 6) These conceptions are no longer tenable. The first case could be shown to be an instance of dissociation with interference (*see* below), the second was found by Wenckebach himself not to be amenable to a satisfactory analysis by the methods then available He considered, however, the possibility that extrasystoles are caused by interference of two " autochthonous rhythms " (Wenckebach, 1907)

That the common bigeminal pulse may be due to the interference of two rhythms was mentioned by several writers (for example, Lauder Brunton, Siciliano), but without any proof for this conception Cushny, as a result of experimental observations, wrote that it was tempting to assume such a mechanism in the common clinical variety of bigeminal action, but declared it was " surrounded with difficulties " and adhered to the view that the extrasystole in the bigeminal heart action is in some way the result of the previous contraction

Fleming (1912) seems to have been the first to explain in more detail extrasystoles with accurate coupling as resulting from the activity of an independent ventricular centre of impulse formation By measuring venous and radial tracings he found that the extrasystoles occurred in one record every 1·8 second and in another every 1·6 second, the ventricular rate of the independently beating ventricles being 30–40, and concluded: "This at once suggests that the ventricles are following a rhythm set by two pacemakers, one at the sino-auricular node, producing physiological beats, and another at an irritable focus in the ventricle, which is rhythmically discharging stimuli at the customary rate of ventricular stimulus production, thus giving rise to extrasystoles". Fleming already recognized that such a conception would make it difficult to explain the presence of a compensatory post-extrasystolic interval, since the faster sino-auricular impulses would be expected to destroy the immature impulse in the automatic ventricular centre. This "apparent difficulty might be explained by supposing that the irritable focus in the ventricle, which gives rise to rhythmical extrasystoles, lies in what may be called a backwater of the primitive cardiac tissue, and while stimuli can stream down this backwater, physiological stimuli passing down the main channel are unable to disturb the point where ventricular stimuli arise." Fleming's paper does not seem to have attracted much attention at the time and his remarks are quoted, not only because they are of a certain historical interest, but also because they foreshadow one of the main problems which later gave rise to a good deal of controversy, namely, the application of this theory to the explanation of extrasystoles with accurate coupling.

The development of this conception that extrasystoles are due to the rhythmic activity of an ectopic centre is due to Kaufmann and Rothberger's series of important papers published between 1917 and 1923. The starting point was an accidental observation (1917): In experiments on dogs and cats, which had been undertaken in order to study auricular extrasystoles artificially produced in different phases of diastole, rhythmical stimulation of the *auricles* with a rate different from the spontaneous heart rate produced extrasystoles *which, contrary to expectation, were accurately coupled to the preceding physiological* beat This was due to the fact that the extrasystoles were conducted to the sino-auricular node, thereby producing a shift of the S-A rhythm The two rhythms are therefore linked by this shift of the S-A rhythm. The number of extrasystoles depended on the relation between the rate of the S-A rhythm and that of artificial stimulation.

Rhythmical stimulation of the *ventricles*, on the other hand, produced a different kind of arrhythmia Since ventricular ectopic impulses are not usually conducted backwards to the S-A node, the S-A rhythm proceeds undisturbed by the extrasystoles which, therefore, occurred at different phases of diastole, in other words with varying coupling With ventricular extrasystoles, too, an allorhythmia occurred, that is, an arrhythmia consisting of recurring identical groups of normal and ectopic beats The number of sino-auricular and that of ectopic beats in each group depended on the relation between the rates of the sino-auricular and that of the ectopic rhythm, such groups were far more complicated than in the case of auricular extrasystoles, and often two or more ectopic beats followed in succession. When the lowest common multiple of the interval between two successive S-A beats and that between two successive ectopic beats was reached, the same grouping started afresh. The same considerations hold good for those auricular extrasystoles which are not conducted backward to the S-A node, but are followed by a compensatory post-extrasystolic interval.

The further development of this conception and its application to clinical cases (Kaufmann and Rothberger, 1919a, 1920a) led these authors to postulate the following conditions by way of underlying mechanism:

1. If an ectopic centre produces rhythmic impulses with a rate lower than that of the S-A node it has to be postulated that the ectopic centre is guarded against the destruction, by the faster S-A stimuli, of its impulses; Kaufmann and Rothberger termed this mechanism "protective block" or entrance block

2. If an ectopic centre produces impulses with a rate higher than the S-A rate, an ectopic rhythm or ectopic tachycardia would result unless some of the ectopic impulses were prevented from becoming effective A blocking of such impulses between the centre of their formation and the myocardium, termed " exit block ", was therefore postulated Such exit block would be additional to the protective block, the presence of which has to be postulated also in this variety of parasystole, since the normal rhythm does not influence that of the ectopic centre.

While it will be shown below that this conception of a rhythmic activity of an ectopic centre proved most fruitful for the analysis of certain rare cases of ectopic arrhythmias, it must be emphasized that Kaufmann and Rothberger's attempt to explain by this hypothesis the clinically common form of extrasystolic arrhythmias with accurate coupling of the extrasystoles soon met with severe criticism and has now universally been discarded. To postulate as an auxiliary hypothesis, as did Kaufmann and Rothberger (1922) in order to explain the constancy of the coupling of the " extrasystoles ", a tendency of the rates of the normal and the ectopic rhythm to occur in simple mathematical relations to one another, obviously is a *petitio principii* and remains unacceptable, even if in some proved instances of parasystole a certain parallelism between these two rhythms was observed both clinically and experimentally. The current explanation of extrasystoles with accurate coupling was at the time, and still is, that they are in some way precipitated by the preceding beat, and the objection was raised almost immediately against Kaufmann and Rothberger's auxiliary hypothesis that the simple mathematical relationship between the rates of S-A and ectopic rhythm is the *result*, and not the *cause*, of the accurate coupling (Mobitz, Scherf, 1924)

We propose to make a fundamental distinction between ectopic beats with accurate coupling and those not standing in a fixed time relation to the preceding beat Only the former group of ectopic beats, assumed to be in some way precipitated by the preceding beat, should in our opinion be considered extrasystoles in the strict sense of the term The differentiation between extrasystolic and automatic beats is discussed in more detail in the chapter on the mechanism underlying extrasystolic beats.

It was also emphasized that only longer records can be used for analysing the mechanism of ectopic arrhythmias, since interpretations based on short tracings are open to serious fallacies (Iliescu and Sebastiani, Schott, 1927) The criticism of Iliescu and Sebastiani, however, went too far in certain respects, as stated later by Lewis in whose laboratory they worked

Kaufmann and Rothberger's great merit is that, by their painstaking analysis of numerous experimental and clinical records, they established that certain cases of ectopic arrhythmias are due to the co-existence of two independent centres rhythmically discharging effective impulses. This results in an interference of two independent rhythms, the S-A rhythm and the ectopic rhythm, jointly producing an ectopic arrhythmia Such centres are active " side by side "—hence the prefix " para " in parasystole and pararrhythmia

A parasystolic mechanism should be suspected in those cases of ectopic ventricular arrhythmias in which

1. the coupling of the ectopic beats varies,
2. the length of the intervals between two consecutive ectopic beats stand in simple mathematical relations to one another
3. The presence of combination (summation, fusion) beats, showing in the electrocardiogram forms intermediate between those of beats produced by either centre alone, tends to support the diagnosis Such beats are due to the simultaneous or nearly simultaneous activation of the heart by the two centres and therefore are expected to occur at such moments at which an impulse is due from each of the two centres.

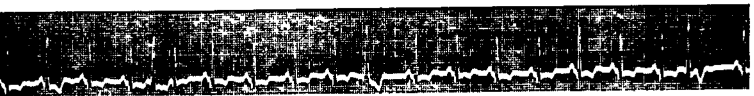
Two main forms of parasystole are recognized. In the first variety, every impulse of either centre becomes effective if it falls outside the refractory period of the preceding contraction. The resulting arrhythmia is termed: parasystole with simple interference The second variety differs from the previous one in that some of the ectopic impulses which fall outside the refractory period of the preceding beat fail to yield a response; such impulses are believed to be blocked in some way between the ectopic centre and the myocardium (or fail to be initiated), and the resulting arrhythmia is therefore termed: parasystole with exit block. In both varieties a protective entrance mechanism guarding the ectopic centre from the impulses of the other centre has to be postulated

Parasystole with Simple Interference of Two Rhythms without Exit Block

This arrhythmia, which was first described by Singer and Winterberg in 1920, may be illustrated by Fig. 101. The record shows sinus rhythm with ectopic beats of ventricular origin The sinus beats are characterized by well-developed P waves preceding at a normal interval the QRS complexes These consist of distinct Q waves and slightly slurred R waves which are followed by distorted S-T segments with inverted T waves. Beats No. 2, 5, 11 and 19 are ventricular ectopic beats, occurring in different phases of diastole; their Q waves are smaller, their R waves higher, wider and more slurred, and their final deflections more deeply inverted. The first ectopic beat (the second beat of the record) occurs so late in diastole that nearly the whole of the P wave of the sinus beat, due at the time, had already been inscribed. The second ectopic beat (Beat No. 5) is interpolated. Beat No. 16 is intermediate in shape between the sinus and ectopic beats, that is, a combination beat, it resembles the sinus beats more than the ectopic ones and it has to be assumed that the ventricles were activated mostly by the sinus impulse [With combination beats the exact time of the occurrence of the ectopic beat cannot be determined. If, as in the case of beat No 16, the combination beat resembles the sinus beats more than the ectopic ones it has to be assumed that the ectopic impulse activated the ventricles a few hundredths of a second later than the sino-auricular one, the reverse holds good for combination beats approximating, in the electrocardiogram, the appearance of the ectopic ones, in which case the ectopic impulse must have become effective in the ventricle slightly in advance of the sino-auricular one. A more accurate determination of the time relations in combination beats between the conducted and the ectopic impulses was possible in a case with right bundle branch block, in which the ectopic centre was situated in the right ventricle (Vedoya, 1946).]

The occurrence of the ectopic beats in various phases of diastole, that is, the varying coupling, and the presence of combination beats suggest the possibility of a parasystolic origin of the ectopic beats and measurement confirms it, since it proves the rhythmic activity of the ectopic centre The sinus rhythm has a cycle length of 0 74–0 78 second (rate 77–81 per minute) The interval between the first and second ectopic beats (Beats No. 2 and 5), which are separated by two sinus beats, measures 1·97 seconds, the longer intervals between the second and third (Beats No 5 and 11) and that between the third and fourth (Beats No 11 and 16) ectopic beats are 3·94 and 3 92 seconds, that is, double the interval between the first and second one. The interval between the last two ectopic beats (Beats No. 16 and 19) equals that between the first two (1·98) It follows that the inter-ectopic intervals* measured 1·97–1·98 seconds or a multiple of that length (double); measurement also shows that all ectopic beats which fall outside the refractory phase of sinus beats yield a response, just as all sinus impulses occurring outside the refractory phase of the ectopic beats become manifest. In long records of this patient these conditions were found to be invariably

* Inter-ectopic intervals are the intervals between two consecutive ectopic beats separated by one or more intervening sino-auricular beats Ectopic cycle length, as used below in this chapter, is defined as the interval between two ectopic beats following in succession



78 75 78 76 76 76 76 75 75 76 74 76 74 75 75 75 74 74
74 78 78 41 41 69 76 76 75 57 94 74 76 74 74 76 75 47 101
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Fig 101 —Lead 2 Parasystole with simple interference The diagram below the tracing illustrates the mechanism of the arrhythmia The figures indicate intervals in hundredths of a second (except the bottom row which indicates consecutive numbers of ventricular beats)

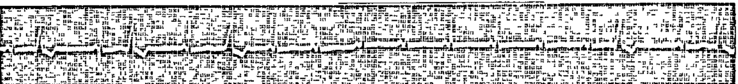


Fig 102 —Lead 2. Parasystole with simple interference

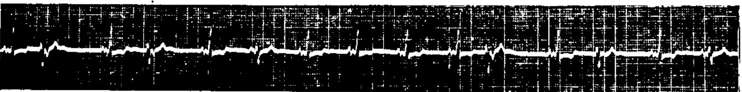


Fig 103 —Lead 2 Parasystole with retrograde conduction of some automatic beats

present, and the assumption is thus justified that the arrhythmia is due to the interference between the sino-auricular and a slower independent ectopic ventricular rhythm (shortest inter-ectopic interval 1·96 seconds, corresponding to a rate of about 30 per minute).

Fig. 102, obtained in a case of hypertension, illustrates a similar condition At first sight the record might give the impression of the common variety of extrasystoles, but closer inspection reveals that the coupling of the " extrasystoles " varies Disregarding the middle portion of the reproduced record, its measurement as well as that of other tracings of the same patient shows that the inter-ectopic intervals varied between 1·68 and 1·74 seconds, the cycle length of the sinus rhythm between 0 80 and 0·84 second. The long interval between the third and the fourth ectopic beats in Fig. 102 measures 6·98 seconds, that is four times 1·74 Three intervening ectopic impulses failed to yield a contraction because, as measurement shows, they occurred during periods in which the ventricles were in the refractory phase of the preceding sinus beat

Fig 103, obtained from a sixty-six-year-old man with coronary sclerosis, illustrates another instance of parasystole. The diagnosis is suggested by the varying coupling of the ectopic beats, which is immediately apparent, and is confirmed by measurement· The cycle length of the sinus beats is 0·88 second (rate: 68), the inter-ectopic interval 1·98 seconds (rate 31) During the long inter-ectopic interval recorded in the centre of the tracing one ectopic impulse failed to yield a response as it occurred during the refractory period of a sinus beat This long inter-ectopic interval measures 4·10 seconds, and thus is considerably longer than twice the—otherwise constant—inter-ectopic interval of 1·98 seconds. This lengthening of the longer inter-ectopic intervals was invariably encountered in this particular case. A similar observation was reported by Vedoya (1944, Case 3) His tentative explanation of these time relations is mentioned below in this chapter

Another feature of this case is that some of the ectopic beats were conducted in a retrograde direction to the auricles This is evident because of the occurrence of sharply inverted P waves in the ascending limb of the first, second and fourth ectopic beat The observation that such retrograde conduction was confined to those ectopic beats which occurred comparatively early in the diastole of the preceding sinus beat suggests that it is due to the presence of a supernormal phase of conductivity.

This possibility has also to be considered in another observation, illustrated in Fig 104. The record was obtained in a sixty-six-year-old man with alcoholic cirrhosis and advanced coronary sclerosis Parasystole is present, sinus rhythm (cycle length: 0·82–0 88 second, rate 68–73) co-existing with an automatic ectopic ventricular rhythm. The inter-ectopic intervals measure 2·84 seconds on an average (2 80–2 87 seconds; average ectopic rate 21). While generally the post-ectopic intervals are compensatory, on several occasions they are lengthened, with a consequent shift of the sinus rhythm. In Fig 104, three automatic beats are shown The first of these has a coupling of 0 72 second, the post-ectopic interval is compensatory The post-ectopic intervals after the second and third automatic beats are lengthened by 0 06 and 0 08 second, respectively, and the sinus rhythm is shifted accordingly after these beats The T waves of these two automatic beats contain a P′ wave which falls outside the expected sequence of the sinus P waves The most likely explanation seems to be that, on such occasions, the automatic beat was conducted in a [illegible]

phase of conductivity.

Since, in the three foregoing examples, no two ectopic beats occurred in succession, at least one sinus beat being interspersed between them, the rate of ectopic impulse formation could not be directly determined. It is possible, though unlikely in the instances described, that the observed shortest inter-ectopic intervals might be multiples of the ectopic cycle length.

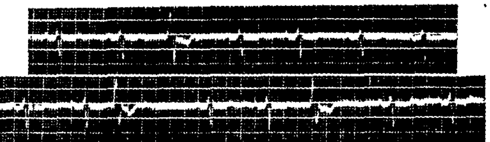


Fig 104 —Lead 3 Parasystole with retrograde conduction of some automatic beats and consequent shift of the sinus rhythm The two records are continuous

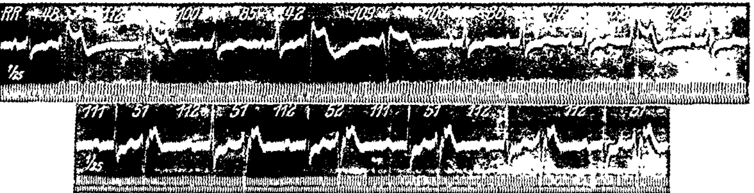


Fig 105 —Lead 2 Top record Parasystole with simple interference and two automatic beats in succession Bottom record Continuous bigeminy with accurately coupled extrasystoles, observed in the same case From Scherf and Schott, 1930 *Klin Wschr*

Fig. 105, top tracing, shows an instance of parasystole with simple interference i two successive ectopic beats occur at two places; the ectopic cycle length, thus measurable, was 1·12 and 1·09 seconds, (rate 53 and 55 per minute), that of the sin 0 84–0·86 second (rate· 70–71 per minute).

Parasystole with simple interference, while uncommon, is perhaps not quite as the small number of published cases would indicate, and might be found more longer records were taken and analysed from this point of view It has been estimat its incidence is about 1 in 1,200 electrocardiograms in a general hospital. In 19 eleven cases could be collected by Faltitschek and Scherf, including five of their o the attached table particulars are given of the forty-nine cases of which we are aw cluding eighteen hitherto unpublished instances, in which we believe the diagnosis been established Only those cases were included in which the diagnosis of para could be made with certainty It will be seen that this arrhythmia was somewha frequent in men than in women; amongst the forty-seven cases, in which the sex in is reported, were thirty-one men.

TABLE 2 VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE

No	Author	Age	Sex	Cardiac Condition	Rate S-A	I
1	SINGER AND WINTERBERG (1920)	20	m	Enlargement left ventricle	71	
2	WINTERBERG (1923)	52	m	Aortitis	92–120	
3	WINTERBERG (1923)	56	f	Arteriosclerosis and Hypertension	92–95	
4	SCHELLONG (1924)	37	m	Nephritis one year previously, circulatory system normal	53–64	
5	ZANDER (1927a)	40	f	Mitral incompetence	92	
6	SCHERF AND SCHOTT (1930)	63	m	Coronary sclerosis	63–96	
7	FALTITSCHEK AND SCHERF (1932)	30	f	Mitral and aortic valv dis	109–117	
8	,, ,,	56	m	Coronary sclerosis	130	
9	,, ,,	63	m	,, ,,	81–92	6
10	,, ,,	47	m	,, ,,	88	
11	,, ,,	33	f	Mitral valvular disease	92	4
12	HOLZMANN (1934)	61	m	Advanced congestive heart failure	64–67	
13	,, ,,	61	f	,, ,, ,, Hypertension, bigeminy	90	
14	,, ,,	76	f	Advanced congestive heart failure, aur fibrillation	—	5
15	ECKEY (1936)	70	m	Advanced congestive heart failure	66	
16	HILL AND CAMERON (1936)	59	m	One month after coronary thrombosis	56–60	4
17	*ECKEY (1937)*	*38*	*f*	*Normal*	*55–69*	4
18	,, ,,	25	m	,, (? familial)	83	
19	,, ,,	54	m	After influenza, mild diabetes	62–68	5
20	VEDOYA AND BATTINI (1939)	12	f	Normal	109–133	13
21	ECKEY (1939)	24	m	After septicaemia Otherwise heart normal	68–80	3
22	,, ,,	18	m	Not stated	67–78	
23	VEDOYA (1944)	50	m	Arteriosclerosis	69–87	5
24	,, ,,	48	m	Normal	74–87	3
25	,, ,,	51	m.	Hypertension	73–100	3
26	HOLZMANN (1945)	72	f	Coronary sclerosis, cong heart failure	71–76	4
27	VEDOYA (1946)	45	m.	Right bundle branch block Syphilis	91–109	3
28	VEDOYA, DUMAS AND URDAPILLETA (1948)	23	f.	After acute gastro-enteritis	51–57	3

VENTRICULAR PARASYSTOLE WITH SIMPLE INTERFERENCE—*Cont*

No	Author	Age	Sex	Cardiac Condition	Rate S-A	Rate Ectop
29	VEDOYA, DUMAS AND URDAPILLETA (1948)	37	f	Normal, but seven months after confinement, toxaemia of pregnancy	*ca*85	50
30	GENTILE (1950)	43	m	Normal, but one month after pneumonia	*ca*60	35–38
31	GALLAVARDIN AND FROMENT (1950)	45	f	Rheumatic mitral valvular disease	60–80	61–63
32	SCHERF AND SCHOTT	68	f	Carc recti	71	50
33	" "	56	m	Coronary sclerosis	78	45
34	" "	53	m	Hypertension	82	50
35	" "	34	f	Mitral stenosis, auric fibrillation	65*	50
36	" "	?	?	Coronary sclerosis, auric fibrillation	82*	41
37	" "	52	m	Hypertension	98	61
38	" "	71	m	Coronary sclerosis	70	44
39	" "	48	m	Hypertension	74	32
40	" "	?	?	Hypertension	84	41
41	" "	69	m	Coronary sclerosis	62	32
42	" "	68	m	" "	71	36
43	" "	70	m	Atheromatosis	75	28
44	" "	74	f	Myocardial infarction	84	31
45	" "	69	m	Hypertension	66	28
46	" "	53	m	Coronary thrombosis	85	34
47	" "	66	m	Coronary sclerosis	68	31
48	" "	66	m	Alcoholic cirrhosis, coronary sclerosis	70	21
49	" "	56	m	Coronary sclerosis	96	50

* Average ventricular rate

The ectopic rate tends to be slow, but may vary between twenty-one and eighty-nine, (disregarding Vedoya and Battini's case which shows exceptionally high S-A and ectopic rates) Some relationship seems to exist between the rates of the two centres: the slow ectopic rhythm of 34 was found in a patient with a sinus rate of 53–64, whereas the fast ectopic rhythm with a rate of 89 occurred in a case in which the sinus rate was 109–117. A similar relationship between the rates of the underlying A-V rhythm and that of an artificially produced ectopic rhythm was also seen experimentally (Scherf, 1926, Scherf and Chick), but clinically, as the table shows, does not hold good for all cases

Changes in rate of the sinus rhythm may be associated with changes in the same direction of the ectopic rate (Scherf and Boyd, 1950)

Diagnosis

The main diagnostic criteria have already been outlined above in this section (p 153), and the varying coupling of the ectopic beats and the simple mathematical relations between the inter-ectopic intervals were stressed as the most important features of this arrhythmia. If the ectopic cycle length is directly measurable and a parasystolic mechanism is to be diagnosed, the inter-ectopic intervals must be multiples of the ectopic cycle length. It was also emphasized that only those cases can be considered to be parasystole with simple interference in which—in addition to the above criteria—it can be shown that all impulses of both the sinus and the ectopic centre, which fall outside the refractory period of the preceding beat, yield responses All these points require some qualifications and amplifications which are also of physiological interest

Coupling. If the ectopic rate is slower than the sinus rate—and this is a prerequisite for

this form of parasystole without exit block, since otherwise the faster ectopic rhythm would dominate the whole heart (regarding two exceptions *see* below)—the longest coupling obviously equals the cycle length of the sinus rhythm. The shortest coupling can, in sufficiently long records, be considered to equal the relative refractory period, that is, the refractory period of the sinus beats for the ectopic impulses in the individual case (Singer and Winterberg). This provides an additional criterion in the analysis of such cases: since the shortest coupling of a manifest ectopic beat equals the relative refractory period, in order for a diagnosis of parasystole with simple interference to be made it has to be demonstrated that the latent couplings of all those ectopic impulses, which calculation shows to have been produced, but which failed to yield a response, were shorter than the shortest manifest coupling of an ectopic beat Occasionally an ectopic impulse calculated to occur with a coupling slightly longer than the shortest manifest coupling fails to yield a contraction, differences up to 0 03 second can be disregarded in this connexion, in view of the variations in the rates of sinus and ectopic rhythms and in the length of the refractory phase, also because of the margins of error of measurement, an exit block need not be assumed in order to explain the failure of such impulses to produce a contraction (*see* Fig. 102)

A glance at Table 2 will show that the ectopic rhythm usually is considerably slower than the sinus rate, in all such cases the arrhythmia manifests itself by occasional ectopic beats, occurring singly or in short groups, the couplings varying considerably in length If, however, the rates of the S-A and of the ectopic rhythm differ but slightly, there is a slow shift between the two rhythms, longer periods of one rhythm alternate with longer periods of the other and in such cases the variation in the length of coupling is small Only three instances of this variety are on record In one of Holzmann's cases (Holzmann, 1934, Case 1), the rate of the sinus rhythm was 64–67 per minute, that of the ectopic ventricular rhythm 60. As a result, there was a slow shift of the two rhythms and the couplings of the ectopic beats varied only between the narrow limits of 0·60 and 0·64 second, that is, within the limits usually accepted for the accurate coupling of the common variety of extrasystoles. Holzmann points out that, in such a case, greater variations in the length of coupling cannot be postulated as a condition for a diagnosis of parasystole, but it should be understood that, while this is justified for the case in question, it is a rare exception This case is remarkable also since, in addition to the two centres described, a third automatic centre produced effective impulses; this was probably situated in the A-V node. The other two cases showing a small difference in the rates of the two rhythms (Eckey, 1936, Vedoya and Battini) present similar features, but are, as far as we are aware, unique in that the rate of the ectopic rhythm was slightly faster than that of the sinus rhythm (*see* table). Parasystole with simple interference—without exit block—with a faster ectopic rhythm is possible only if the difference in rates is very small, since otherwise ectopic rhythm or ectopic tachycardia would obviously result.

An independent ectopic ventricular rhythm interfering with supraventricular beats in auricular fibrillation has been observed in three cases (*see* table).

Ectopic cycle-length and inter-ectopic intervals. (For the definition of these terms, *see* above, p 154) The rate of impulse formation in the ectopic centre can be ascertained with the greatest degree of certainty in those cases in which two ectopic beats follow one another in succession, without a sinus beat intervening, as in Fig 105 In such cases the ectopic rate is directly measurable, and a diagnosis of parasystole is greatly facilitated and can be considered established if the longer intervals between consecutive ectopic beats, which are separated by one or more sinus beats, are multiples of the ectopic cycle length For a variety of reasons, however, the inter-ectopic intervals are not always *exact* multiples of the ectopic cycle length The first reason is that the rate of the ectopic rhythm is not absolutely constant, though usually its variations are smaller than those of the S-A rhythm Moreover, it was found already by Kaufmann and Rothberger and subsequently by others (Singer

and Winterberg, Schott 1927, Holzmann) that the longer inter-ectopic intervals are a little shorter than a multiple of the ectopic cycle length This is due to the fact that, with two ectopic beats following in succession, there is slight delay in the conduction of the second impulse, owing to the greater demands made on the conducting path between the ectopic centre and myocardium by the two impulses following in close succession It follows that the manifest ectopic cycle length, as it is measured as the interval between two successive beats, is lengthened, beyond the interval between the formation of the two impulses, by the increase in the conduction time of the second impulse, this does not occur if, with several sinus beats interspersed in the longer inter-ectopic intervals, a longer recovery period is available for the conduction of the second impulse. There is some evidence that such disturbances of conduction of the ectopic impulse occur: If more than two ectopic beats occur in succession, the intervals between successive beats tend to lengthen (*see* this section, p 164) Zander (1927a) reported a case of ventricular bigeminy in which at times the coupling gradually increased (from 0 44 to 0 56 or 0 58 second), until one extrasystole failed to occur and the subsequent sinus beat was followed by an extrasystole with short coupling and the same phenomenon started anew, that is, Wenckebach's periods in the conduction of the extrasystoles We have observed a similar case (*see* chapter on " Coupling ", p 199) Schott reported a case of parasystole (1927, Case 2) in which the ectopic cycle length was measurable on five occasions, being 0 28–0 29, the longer interval of 0 37 second, which was found at one place, could be shown by calculation to be exactly due to delay in conduction of the second impulse of the ectopic couple

As rare exceptions two observations are on record (Vedoya, 1944, Case 3, case illustrated by Fig 103), in which longer inter-ectopic intervals—containing a greater number of sinus beats—were longer than a simple multiple of shorter ones In a way this is the reverse of the time relations just discussed By way of a tentative explanation Vedoya points out that, in his case, this phenomenon was observed if the ectopic beat terminating the longer inter-ectopic interval had a short coupling to the preceding sinus beat He believes that, in such instances, the conduction time of this ectopic beat was lengthened, owing to the increased demands, upon conduction through partially refractory tissue surrounding the ectopic centre, by two impulses (one S-A, one ectopic) following in quick succession Slight differences in shape of ectopic beats occurring with a short coupling are attributed by him to aberrant conduction of the ectopic impulse through this partially recovered tissue around the centre While Vedoya's view is a plausible explanation for his observation, we do not believe that a structurally altered block zone surrounding the ectopic centre should generally be postulated to explain the protective and exit block In our opinion these phenomena follow more directly from the mechanism of ectopic automatic impulse formation, intensity of S-A and ectopic impulses, and excitability of the ectopic centre at different times These aspects are discussed in more detail below in this chapter and in the chapter on " Mechanism " (p 518)

With these reservations all inter-ectopic intervals must be shown to be multiples of the ectopic cycle length, if parasystole is to be diagnosed This is particularly important in regard to shorter inter-ectopic intervals in which only one or a few sinus beats are interspersed Strict accuracy cannot be expected owing to some variations in the rate of ectopic impulse formation and conduction, which were discussed above, and to the margin of error in measurement

It is obvious that, if a very long inter-ectopic interval is divided into a multiple of the ectopic cycle length, such calculations become useless with intervals beyond a certain length. This limit is reached if the average variations in the length of the ectopic cycle length, multiplied by the number of ectopic cycle lengths supposed to be contained in the long inter-ectopic interval, attain the length of the ectopic cycle length, because any interval exceeding this limit can be shown as a multiple of a whole number and the average ectopic cycle length ±

its maximum variations. Singer and Winterberg, who first pointed out these relations, gave a simple formula for this: $E = x\ (\pm d)$, if E is the average ectopic cycle length, $\pm d$ the maximum variations from this average, and x the number of ectopic cycle lengths in the inter-ectopic interval This means that the greatest number (x) of the cycle lengths in a long inter-ectopic interval, which can be used as supporting a parasystolic origin, is that which, multiplied by the greatest variations (d) from the average of the ectopic cycle length does not exceed the cycle length (E) itself. Mobitz postulated for this even stricter criteria (which are admirably presented by Feher). In practice, it is often possible to dispense with such calculations if the other criteria for diagnosing parasystole are present and particularly if the ectopic cycle length is directly measurable. Greater caution is necessary in cases in which this is not possible and the ectopic cycle length has to be calculated from (shorter and longer) interectopic intervals.

In a remarkable case published by Vedoya, Dumas and Urdapilleta carotid sinus pressure inhibited the sinus rhythm so that the parasystolic ectopic rhythm alone controlled the heart Experimentally, vagal stimulation during parasystole produced by veratrine had the same effect (Scherf and Chick).

Clinical significance

A glance at Table 2 shows that, out of forty-nine recorded cases of this arrhythmia, no fewer than thirty-eight had evidence of pronounced structural heart or cardiovascular disease As far as any conclusions can be drawn from a small series, the assumption seems justified that this association is not coincidental and constitutes but one sign of such structural alterations of the heart.

Auricular parasystole

Parasystole with simple interference between S-A and *auricular* ectopic rhythm is very rare and, as far as we are aware, only four cases are on record in which this diagnosis can be considered established.

The most convincing instance is the case published by Jervell (1932). His patient was a man of twenty-five without any evidence of heart disease in whom the arrhythmia might have been a congenital anomaly The analysis of long records showed parasystole with simple interference between S-A rhythm (cycle length 0·51–0·66 second; average rate 90) a [illegible]
S [illegible]
a [illegible]
intervals were divisible by the smallest inter-ectopic interval which was considered to be the cycle length of ectopic impulse formation, only one sinus beat intervening Nowhere did two ectopic beats follow in succession. The analysis of such a case is more complicated than if the ectopic rhythm is ventricular in origin, since the auricular ectopic beats were usually conducted to the S-A node (as is the rule with auricular extrasystoles), thereby causing a shift in the S-A rhythm. Most of the post-ectopic intervals were therefore not compensatory It could be shown that the auricular ectopic centre was protected against the S-A impulses and that certain variations in the time relations were due to disturbances of conduction [illegible]

[illegible]

with hypertension and coronary sclerosis. There was, at first, 2 : 1 block and an ectopic auricular rhythm interfered with the S-A rhythm, the ectopic rate being a little slower than half the rate of the sinus The ectopic centre was probably situated near the tail of the sinus node. Subsequently the 2 · 1 block disappeared, but the ectopic auricular rhythm continued, giving rise to what appeared to be auricular " extrasystoles "; they had, however, the same

shape in the electrocardiogram and occurred at the same (—P)–(—P) intervals as before so that persistence of the parasystolic origin could be assumed The ectopic centre was protectively blocked, but, as in Jervell's case, the ectopic auricular impulses were conducted to the S-A node so that the post-ectopic intervals were not compensatory

Vedoya (1944, Case 5) published another instance of this rare arrhythmia It was observed in a man of thirty-five without any evidence of cardiovascular disease. The rate of the sinus rhythm varied between 65 and 81 per minute Frequent auricular ectopic beats were recorded, the coupling of which varied between 0 49 and 0 85 second. Measurement showed the inter-ectopic intervals to be divisible by 1 15–1 24 (average 1·20) and a coexisting auricular ectopic rhythm could thus be demonstrated The presence of auricular combination beats supported the diagnosis of auricular parasystole In this case, too, the ectopic auricular impulses were conducted to the S-A node, producing a shift of the sinus rhythm.

Another possible instance of auricular parasystole is one of Kaufmann and Rothberger's cases (1920a) (Case T M No 881, also same authors, 1923)

We have observed only one case of auricular parasystole It concerned a fifty-nine-year-old man with a fresh antero-septal infarction due to coronary thrombosis The patient had

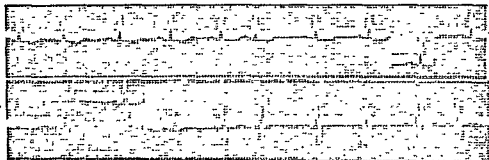


FIG 106 —Leads 1 and 3 Auricular parasystole

received 0 2 gramme of folia digitalis for 8 days Fig 106 shows lead 1 and 3 The second and sixth beats in lead 1, the second, sixth and tenth beats in lead 3 represent auricular ectopic beats The coupling varies In the two tracings reproduced in Fig 106, the inter-ectopic intervals measure 2 69, 2·68 and 2·84 seconds respectively In another record they were 2·68, 2·68 and 2·73 seconds

Ventricular parasystole with ectopic centre above the bifurcation of the bundle of His

A unique observation of this form of parasystole has been described by Scherf and Boyd (1950) One of the tracings obtained in that patient, a man of seventy with pernicious anaemia, is reproduced in Fig 107 It shows sinus rhythm, rate about 70, with lengthened P-R intervals (about 0 44 second) Premature beats having the

ute The analysis of other tracings of this patient shows, however, that this interval of 2·58 seconds actually included two cycle lengths of the ectopic rhythm, the rate of which is therefore 46 per minute In the reproduced record only every second ectopic impulse yields a contraction since the remaining ones occurred during the refractory period of the ventricles

A parasystolic arrhythmia has therefore to be assumed in which a sinus rhythm of a rate about 70 co-exists with an ectopic rhythm of a rate of 46. Because of the fact that the opic beats have the same shape as the sinus beats the ectopic centre has to be located ove the bifurcation of the bundle of His, that is, in the A-V node or the main bundle .is also accounts for the absence of combination beats: the sinus, as well as the ectopic pulses traversed the same paths in the ventricles. The ectopic centre was generally pro- :ted *against the sinus impulses, though occasionally* sinus impulses, occurring at certain ervals after a preceding ectopic beat, had to be assumed temporarily to abolish such otective mechanism (*see* original paper)

Parasystole with exit block

This variety differs from the preceding one of parasystole with simple interference in the e respect that some of the ectopic impulses, which fall outside the refractory period of the eceding beat, fail to yield a response. In order to explain this phenomenon it is assumed it such impulses are in some way blocked between the centre of ectopic impulse formation d the myocardium; this mechanism was termed exit block (Austrittsblockierung) by iufmann and Rothberger (1919a, 1920a) Such a mechanism has to be postulated in those ses of parasystole in which the rate of ectopic impulse formation is materially faster than : S-A rate, since otherwise an ectopic rhythm or ectopic tachycardia would result

The idea that, clinically, in some cases an ectopic arrhythmia may be due to a para- stolic mechanism with exit block of some of the ectopic impulses tended to be supported the early observations of Kaufmann and Rothberger (1919a, 1920a, Case 4) that in tients with attacks of paroxysmal tachycardia the interval between single isolated extra- stoles outside the attacks were multiples of the interval between successive ectopic beats iring the attacks It is noteworthy that, while for the authors' original cases this inter- etation has long ceased to be acceptable since they were cases with accurate coupling of e ectopic beats (true extrasystoles), the idea of a parasystolic mechanism with exit block .s proved most fruitful in the analysis of other cases and thrown light on certain aspects impulse conduction

A clear instance of exit block is shown in Fig 108 It shows two sinus beats separated, id followed, by groups of two ectopic beats following in succession at intervals varying :tween 0 44 and 0 48 second Two such couples are seen between the two sinus beats and e interval of 0·96 second between the couples is double the interval between the two ec- pic beats of the first couple A second longer interval between couples of ectopic beats, easuring 0·92 second, is seen between the first and second couple following the second nus beat and here again its length is twice that of the interval between successive ectopic :ats. These longer intervals are obviously due to the failure of one ectopic impulse to eld a response The case is noteworthy in that the ectopic rate is directly measurable. Ioreover, the last group of three successive ectopic beats reveals evidence of disturbances conduction of the ectopic impulse, the interval between the last two beats of the group iving increased to 0·52 second from that between the first two beats which is 0·46 second.

An example of parasystole with exit block is given in Fig. 109, obtained from a patient ith hypertension. It shows interference between S-A rhythm with a cycle length of 0 67 ate: about 88) and a slower ventricular automatic rhythm (cycle length 1·25–1·28, rate 7–48) The couplings of the ectopic beats vary. The ectopic centre is protected against ie S-A impulses The longer intervals between the second and third, and the third and

eld a response, and the conclusion is warranted that this is due to an exit block operating

FIG 107—Lead 2 The two strips are continuous Parasystole with ectopic focus above the bifurcation of the bundle of His

48 96 45 44 92 46 52

FIG 108—Lead 3 Exit block during ventricular tachycardia Time base 0 04 sec The figures indicate intervals in sec./100

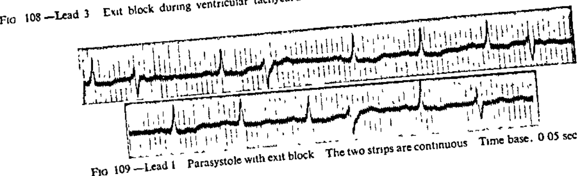


FIG 109—Lead 1 Parasystole with exit block The two strips are continuous Time base. 0 05 sec

on these two occasions The phenomenon of supernormal phase may be responsible for the appearance of ectopic beats only in the early diastole after sinus beats

An exit block has to be assumed in those cases of parasystole in which the ectopic cycle length is shorter than the compensatory pause after an automatic beat, since otherwise two ectopic beats would follow in succession. An observation shortly reported by Schott (1949) may illustrate this (Fig 110 and Table 3) It was obtained from a seventy-six-year-old

TABLE 3

No	R-R	Coupling plus post-ectopic Interval	Inter-ectopic Interval	No	R-R	Coupling plus post-ectopic Interval	Inter-ectopic Interval
1	103			24	**65**	205 =	
2	103			25	140	2 × 102·5	
3	**61**	200 =		26	102		301 =
4	139	2 × 100		27	**59**	203 =	5 × 60
5	104			28	144	2 × 101·5	
6	103			29	100		
7	102		828 =	30	97		
8	105		14 × 59	31	98		591 =
9	104			32	98		10 × 59
10	104			33	**54**	199 =	
11	**67**	209 =		34	145	2 × 99·5	240 =
12	142	2 × 104·5		35	**95**	207 =	4 × 60
13	106			36	112	2 × 103·5	
14	101			37	101		309 =
15	104		843 =	38	**96**	204 =	5 × 62
16	104		14 × 60	39	108	2 × 102	
17	103			40	101		497 =
18	103			41	104		8 × 62
19	**80**	208 =		42	104		
20	128	2 × 104		43	**80**	206 =	
21	102			44	126	2 × 103	
22	103			45	106		
23	99		597 =				
24	**65**		10 × 60				

The coupling of the ectopic beats is shown in bold figures
Time relations of a case of parasystole with exit block Lead CR-3 (From SCHOTT, 1949)

woman with hypertension, a fortnight after a second and five-and-a-half months after the first attack of coronary thrombosis It shows interference between S-A rhythm (cycle length 0·97–1·06, rate 56–62) and a ventricular ectopic rhythm. All inter-ectopic intervals were divisible by 59–62, indicating a rate of ectopic impulse formation of 97–101 per minute An exit block has to be postulated, since otherwise an ectopic tachycardia would have resulted It is also seen that the majority of the compensatory post-ectopic intervals (measuring 1·08–1·45 second) greatly exceed the ectopic cycle length

Other cases of parasystole with exit block are Case 6 of Faltitschek and Scherf, and a case of Feher in which auricular flutter was present

Intermittent parasystole

Intermittent parasystole is defined as a parasystolic arrhythmia in which the ectopic centre produces manifest impulses only intermittently so that the arrhythmia occurs only periodically. On the grounds of experimental observations such periodical activity of a parasystolic centre was postulated by Scherf in 1926 (*see* below, p 171), and two clinical

ates
eats

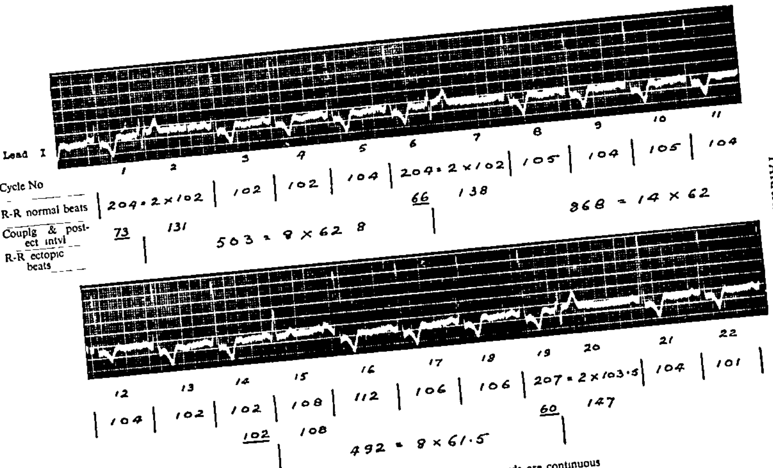


FIG 110—Lead 1. Parasystole with exit block The two records are continuous

which in turn are succeeded by a series of abnormal ventricular complexes. The bottom record illustrates essentially the same condition, except for the arrhythmia's appearing somewhat more complicated The analysis of this case, for the details of which the reader is referred to the original paper, showed the arrhythmia to be parasystole between sinus rhythm and an ectopic ventricular rhythm (rates per minute· top record: sinus 90, ectopic 80, bottom record sinus 80, ectopic 75). Certain beats, also of abnormal shape, which interfere with the otherwise regular sequence of the ectopic rhythm could be shown to have been sinus beats with aberrant intra-ventricular conduction Since the ectopic rhythm proceeds undisturbed by the sinus beats the ectopic centre has to be assumed to have been protectively " blocked "

The further observation, made in both cases, that invariably the first ectopic beat of each series was accurately coupled to the preceding sinus beat suggests that the latter initiated



FIG 111.—Intermittent parasystole The two upper and the two lower strips are continuous Time base 0 05 sec

the ectopic arrhythmia in a manner as yet unknown This relationship thus demonstrates another mode of connexion between parasystolic, that is automatic, and extrasystolic, that is dependent, impulse formation Further instances of such connexion are discussed below in this chapter and its significance in the chapter on " Mechanism " (pp 495, 519)

The Protective "Block". Exit Block

in those cases of parasystole in which the rate of ectopic impulse formation is higher than the sinus rate and/or in which not every ectopic impulse calculated to reach the myocardium outside the refractory period of the preceding beat yields a response Both, however, con- ... vicinity of the ectopic centre, though in ... hese two phenomena have in common,

When certain kinds of arrhythmia were first explained as a result of dissociation between auricles or within the S-A node (Wenckebach, 1906, 1907, 1914, pp 99 *seq*), no explanation of the underlying mechanism was attempted As early as 1912 Fleming, in his paper already quoted, foreshadowed later developments by considering the ventricular ectopic focus to be situated in a " backwater ", supposed to be inaccessible to the physiological stimuli passing along the main stream (*see* above in this chapter, p. 152). Kaufmann and Rothberger introduced the term " protective block " (Schutzblockierung), placing it somewhere near the ectopic centre (1919a, p 233) and considering it to be analogous to the conditions prevailing in cases of complete A-V block (1920a, p 40) Similar views were held by Winterberg and by Schellong, but contested by others (de Boer, Griffith) There is, however, no doubt that a protection of the parasystolic centre exists and it has been conclusively proved experimentally.

When Kaufmann and Rothberger first put forward the conception of a protective block (1919a, p 233) they based it on the observation of Rothberger and Winterberg, made in experiments on dogs, that during ectopic ventricular rhythm auricular extrasystoles may be followed by compensatory intervals This is only possible if the ectopic ventricular centre proceeded in its rhythmicity undisturbed by the extrasystole, that is, was protected against the intrusion of the auricular extrasystole on its way to the ventricles De Boer objected that this observation does not require the assumption of a protective block, but could be explained by the fact that, at the time the ectopic ventricular centre was reached by the extrasystole, it was forming the next impulse and thereby refractory to the excitation wave of the extrasystole, however, this objection, though actually admitting some kind of "block", is certainly not valid for such cases in which a slow independent ventricular pacemaker is active (Wenckebach and Winterberg) Subsequent experimental work demonstrated the presence of a protective mechanism beyond any reasonable doubt

Such investigations became only possible when a method was found experimentally to produce longer chains of ventricular ectopic beats at a comparatively slow rate and originating from one focus This was achieved by electrical or mechanical stimulation of the surface of the exposed heart of dogs in whom the sinus node was clamped and both vagi were cut and who had been given quinine (Scherf, 1926) Long chains of ectopic beats were found to persist after such stimulation, particularly if the normal pacemaker was inhibited by simultaneous vagal stimulation (Scherf, 1927) It could be established that such ectopic beats originated in a circumscribed focus, since the shape in the electrocardiogram of such beats depended on the site of stimulation (1926) and their rate increased by warming their site of origin (1927) Proof that such an ectopic centre of impulse formation was protectively blocked against other impulses could be adduced in several ways

Fig 112 illustrates one such experiment 0·4 gramme of quinine had been given intravenously, both vagi were cut and a few minutes before the reproduced record was taken the clamps had been removed from the sinus node, sinus rhythm returning very shortly afterwards The right ventricle was stimulated by a series of induction shocks and thirteen right-ventricular ectopic beats resulted, the last three of which are reproduced as the first beats in Fig 112 Two spontaneous ectopic beats originating in the same focus followed, at intervals of 0·6 and 0 54 second respectively The next three beats are sinus beats, the first of which shows a P-R interval lengthened to 0·2 from the normal, in this experiment, of 0·1 second This group is followed by one of six right-ventricular beats of the same shape as the previous ones, the ectopic rhythm re-appearing spontaneously. This group is again succeeded by one of three sinus beats, followed in its turn by another of five right-ventricular ones The ectopic cycle length was, on an average, 0·5 second and the intervals taken up by the periods of transient sinus rhythm measured 2 05, 1·98 and 2 02 seconds, that is, four times the interval between successive ectopic beats Owing to the occurrence of three sinus beats, three ectopic beats failed to yield a response, but the rhythmic activity of the

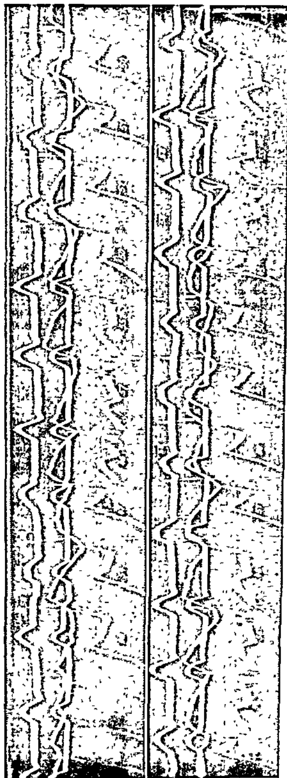


FIG 112.—Parasystole with simple interference experimentally obtained in a dog Tracings from above downward indicate, signal (stimulation), suspension records of *right auricle, left auricle, right ventricle*; electrocardiogram, time base 0 02 sec. From SCHERF, 1926, *Z. ges exp Med*

ectopic centre proceeded undisturbed by the sinus beats and the first manifest ectopic beat after the sinus beats occurred at precisely the moment at which it would be expected, had no interruption of the chain of ectopic beats taken place This record also illustrates the experimental production of parasystole with simple interference between two rhythms The arrhythmia may periodically be elicited again, the rhythm being regular in the interval; the term " intermittent parasystole " was suggested for this condition (Scherf, 1926)

In this example the ectopic rhythm came and went spontaneously due to interference by the sinus rhythm In other experiments the ectopic rhythm was artificially interrupted by producing, by means of induction shocks, a second ectopic rhythm originating in the contralateral ventricle. This resulted in some ectopic beats of the contralateral ventricle during stimulation, followed by a certain number of spontaneous ectopic beats originating in the same focus in this same contralateral ventricle, the original ectopic rhythm subsequently

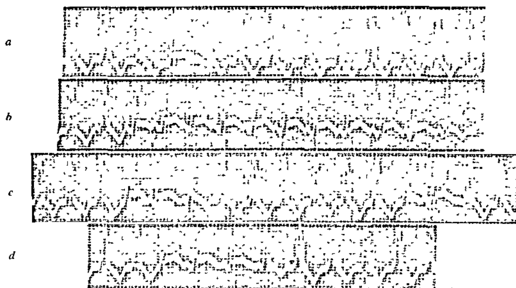


FIG 113 —Parasystole with simple interference produced in a dog by the topical application to the heart of sodium chloride The four strips are continuous

being re-established In such experiments it was invariably found that the interval in the original rhythm between the last beat before the interruption and the first beat of the re-established rhythm after the interruption equalled exactly a multiple of the cycle length of the original ectopic rhythm, or differed from it by half a cycle length, but intermediate figures were never found The significance of the difference by half a cycle length will be discussed below, in the present context it may be disregarded The conclusion is therefore warranted that, during the artificially produced ectopic rhythm of the contralateral ventricle, the ectopic focus producing the original rhythm continued undisturbed by the impulses originating in the other ventricle, that is, was protectively blocked against them (Scherf, 1926)

Similar results were obtained if the heart was sensitized with small doses of barium and a ventricle electrically stimulated, slowing of the sinus rhythm by vagal stimulation favoured the occurrence of ectopic rhythms and similar time relations were observed (Scherf, 1927)

The same conclusions were arrived at in experiments undertaken with an entirely different method It had been shown by Piccione and Scherf that ectopic beats and ectopic rhythms can be produced by the sub-epicardial injection of 0·1 cc of a 10 per cent solution of NaCl Fig 113 is taken from such an experiment and shows an ectopic ventricular tachycardia elicited in this way from the conus of the right ventricle. The ectopic rhythm was interrupted at times by a variable number of sinus beats. The four reproduced strips, marked *a–d*, are continuous. In the two upper tracings the ectopic cycle length is 0 36 second with remarkable constancy In the top tracing the ectopic rhythm is interrupted by one sinus beat and the interval between the last ectopic beat before, and the first ectopic beat after, the sinus beat measures 0·72 second, that is, exactly double the ectopic cycle length. The long interval interrupting the ectopic rhythm in strip *b* measures 4·08 seconds (that is 11 times 0·37) In strip *c* the ectopic cycle length had decreased to 0·34 second and the two intervals during which sinus (or combination) beats intervened measure 1·37 seconds (= 4 × 0·342) and 1 00 (= 3 × 0 333) In the bottom strip *d* the ectopic cycle length had increased again to 0·36 second and the interval taken up by the sinus rhythm measures 1·44 seconds (= 4 × 0·36) These measurements show that, whenever the ectopic rhythm was interrupted by sinus rhythm, the first ectopic beat recurred at a time when it would have been *due without interruption of the ectopic rhythm, that is, throughout the intervening sinus* rhythm the ectopic centre retained its rhythmical activity, being guarded against extraneous (sinus) impulses by protective block The presence of combination beats is a further proof of the parasystolic character of this arrhythmia

In certain experimental conditions (aconitine intoxication and mechanical stimulation), in which two ectopic ventricular rhythms interfered with one another, a double protective block, that is, a block protecting each of the two centres against the impulses of the other, could be demonstrated (Scherf, 1930)

While in such experiments parasystole was observed only occasionally, in a recent series of experiments Scherf and Chick found that topical application of veratrine to the ventricular surface invariably gave rise to parasystolic arrhythmias in which the ectopic centre was protectively blocked

Fig. 114 was obtained from such an experiment Immediately after application of a 0·5 per cent solution of veratrine alkaloid to the conus of the right ventricle an ectopic tachycardia was recorded which interfered with the sinus rhythm. The intervals between the last ectopic beat of one, and the first of the subsequent, group were always multiples of the ectopic cycle length Combination beats occurred frequently.

The nature of this protective block has been extensively discussed No single mechanism was found that could be considered responsible for it in all cases

Some kind of a block zone surrounding in some way the centre of ectopic impulse formation was early postulated (*see* above) and is still assumed in more recent work (Doumer, Vedoya 1944, Katz). With this conception the same area of block was invoked to account for the exit block, a more detailed diagrammatic view of its supposed structure is contained in Doumer's and Vedoya's papers The latter developed an ingenious conception of two zones of refractory tissue surrounding the ectopic centre whereby the degree of refractoriness of the zone closest to the centre (Zone B) is greater than that situated more peripherally (Zone A) The duration of refractoriness of Zone A is assumed to be less than the cycle length of the sinus rhythm, that of Zone B to be longer and only slightly less than the ectopic cycle length Vedoya shows diagrammatically that such conception would explain [illegible]

p. 174). It has to be conceded that a zone of such or a similar kind may exist in some cases. not only was the presence of an area of depressed conduction made most probable by

histological findings in some cases of retrograde conduction of automatic ventricular impulses in cases of complete A-V block (*see* p 138) and considered likely in cases of return extrasystoles (*see* p 120), but also the location of that area could be shown to be of paramount importance; the relation between such arrhythmias and unidirectional block is discussed in the appropriate sections. Similar areas may well exist, in certain cases of parasystole, in the vicinity of the ectopic centre

It is, however, difficult to imagine a block zone, spherically surrounding the ectopic centre, and being of a kind that it prevents impulses from reaching the centre from every direction whereas the ectopic impulses could pass this zone in the opposite direction Wachstein's observations of interference of two or more rhythms and of interpolated extrasystoles in isolated Purkinje fibres show that, whatever the nature of the " block " is, it is, or at least can be, situated in a very small area Faltitschek and Scherf located it in the cell, or group of cells, forming the ectopic centre and pointed out that it will depend on the intensity of the S-A impulses on the one hand and the irritability of the centre itself whether the S-A impulses will break into the centre, in a similar way they attributed the presence or otherwise of exit block to the intensity of the automatic ectopic impulse and the irritability of the tissue surrounding the centre Goldenberg, Gottdenker and Rothberger found in Purkinje fibres of dogs that condenser discharges stimulating the whole fibre did not disturb the rhythmical spontaneous activity of one of several centres and concluded that the condenser discharges were sub-threshold for this centre Again, the emphasis is on the relation between strength of stimulus and excitability of the ectopic centre This conception received further support by the more recent observations of Scherf and Boyd (1950), discussed above. They indicated that the ectopic centre can be protected, either because the stimuli of the other centre are below the threshold necessary to excite the cells of the ectopic centre, or because the ectopic centre is less excitable In one particular case (Scherf and Boyd, 1950, Case 1) the assumption was justified that only during a temporary increase in excitability of the ectopic centre, namely its supernormal phase after emission of an impulse, could it be reached by the sinus impulses Because of all these considerations we prefer the term " protection " to " protective block "

One difficulty which is encountered if the processes in the centre are visualized more closely in conjunction with the membrane theory of initiation and conduction of impulses, and some suggestions about

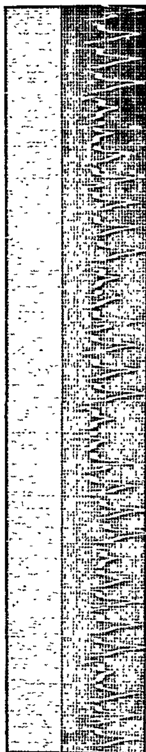


Fig 114 —Parasystole with simple interference produced in a dog by the topical application to the heart of veratrine.

a possible solution of this problem are discussed in the chapter on " Mechanism " (p 518)

While the assumption of some particular kind of blocking mechanism, whether structural or functional, seems necessary to explain the protection of the ectopic centre in cases in which the automatic rhythm is slow, this is not necessary in instances in which the automatic rhythm is fast If the ectopic centre produces impulses at a high rate, this itself would account both for the protective and the exit block, since the centre would be surrounded by refractory tissue as a result of its fast impulse formation. There are good reasons for assuming that in some cases this is the underlying mechanism, and that the rate of impulse formation in the ectopic centre is actually higher than the record as such would seem to indicate

Thus it was pointed out above (p. 171) that, if a chain of ectopic beats was interrupted by an artificially produced number of ectopic beats of the contralateral ventricle, the interval between the last beat of the original rhythm before, and its first beat after, its interruption always equalled a multiple of its cycle length, *or differed from it by half a cycle length* From this it can be concluded that the actual rate of ectopic impulse formation was twice that indicated in the record, every second impulse being blocked In other experiments irregular ectopic arrhythmias were seen which could best be interpreted by the assumption of a faster underlying ectopic rhythm with 3 . 2 or 2 1 block between the centre and myocardium, or a degree of impairment of conduction analogous to dropped beats (Scherf, 1926). Clinical examples indicating disturbances of conduction of the ectopic impulse were mentioned above (pp. 161 and 164), but the most convincing instance in this connexion is a case published by Rosenbluth and Winterberg. Their patient, a thirty-nine-year-old man, showed A-V extrasystoles and attacks of A-V paroxysmal tachycardia In one of such attacks a sudden doubling of the rate was recorded (from 83 to 166 per minute), and the obvious interpretation is that, with the slower rate, a 2 1 exit block had been present. Outside the attack a slower ectopic A-V rhythm, producing beats with the same shape in the electrocardiogram as those during the attacks, interfered with S-A rhythm, the couplings of the ectopic beats varying between 0·38 and 0·76 second, and it could be shown on one occasion that, after an attack, isolated A-V ectopic beats occurred at intervals which were multiples of the ectopic cycle length during the rapid phase of tachycardia

Fig 115 provides another example, obtained in an experiment on a dog (Scherf). At the beginning of the record a series of eight ectopic beats is shown, elicited in the way described above (p 169) and following one another at intervals of 0·22 second (rate: 272 per minute) The rate suddenly dropped to 108 (cycle length 0·55 second). This abrupt change in rate is best explained by a sudden blocking of the ectopic impulses The difference in the height of the three ectopic impulses during slower rhythm, as compared with the beginning of the record, can be attributed to the pronounced change in rate and does not indicate a change of focus of origin.

Failure of impulses to be initiated may also have to be considered as possibly accounting for the change in rate by simple multiples of ectopic rhythms This mechanism has been found in the local oscillatory responses of giant squid nerves in certain experimental conditions (*see* chapter on " Mechanism ", p 510).

Parasystole and Extrasystoles with Fixed Coupling

It was pointed out that, if an independent ventricular ectopic centre produces impulses which interfere with the S-A rhythm, the coupling of such ectopic beats to the preceding beat necessarily varies and that (with very rare exceptions) the varying coupling is one of the cardinal features of this arrhythmia, which distinguishes it from the common variety of extrasystoles with fixed (or accurate) coupling. In very few cases it could be observed that a

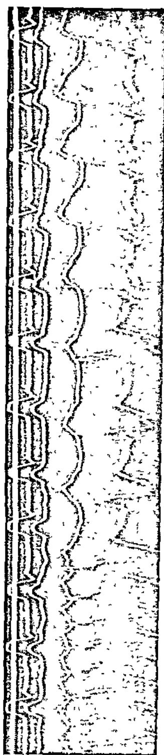


FIG 115.—Exit block recorded in a dog Tracings from above downward indicate signal (stimulation), suspension records of right auricle, left auricle, right ventricle, electrocardiogram, time base 0 02 sec

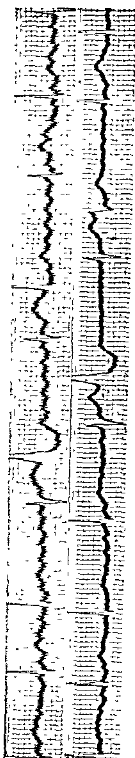


FIG. 116.—Parasystole and extrasystoles which occurred only after automatic beats, observed during auricular flutter (top record) and auricular fibrillation (bottom record)

parasystole with simple interference changed into an extrasystolic arrhythmia with fixed coupling of the extrasystoles (Scherf and Schott, 1930, Rothberger, 1931, p. 675, Vedoya and Battini) Thus Fig 105 shows in its top tracing parasystole with simple interference, the ectopic cycle length being directly measurable (1·09–1·12 seconds) and the couplings of the ectopic beats varying between 0·42 and 0 67 second. Other records of the same patient established the parasystolic mechanism of the arrhythmia beyond doubt, the ectopic cycle length being measurable in five places at 1·12 seconds, the rate of the sinus rhythm varying between 64 and 98 and the couplings between 0 42 and 0·69 second Shortly afterwards continuous bigeminy was recorded, the extrasystoles had the same shape in the electrocardiogram and were accurately coupled to the preceding beat, the coupling being 0 51 second (*see* Fig 105, bottom strip) and, in a longer record comprising 31 beats, varying only between 0 50 and 0 52 second This change in the arrhythmia was probably due to the continuing digitalis treatment resulting in disappearance of the protection of the ectopic centre

Vedoya and Battini's case is of special interest since it shows various changes in the kind of arrhythmia, the combination of which is extremely rare In their patient, a girl of twelve, there was first parasystole with simple interference between an S-A rhythm with a cycle length of 0 45–0 55 second (rate 109–133 per minute) and an idioventricular rhythm which was a little faster (cycle length 0 43–0 45 second, rate 133–139 per minute) The small difference in the rate of the two rhythms resulted in their slow shift At several places unusually long intervals were noticed when a ventricular automatic beat failed to occur at a time it was due, this was attributed to an exit block * It was then observed that at times a ventricular automatic beat was followed by an extrasystole of the same shape in the electrocardiogram, with a coupling of 0 39 second (their Fig 5) or by what appeared to be a combination beat (their Fig 6) Subsequently the ventricular automatic beats disappeared and a bigeminy was recorded with extrasystoles which had identical shape and were accurately coupled to the preceding sinus beat with the same coupling which they previously had in connexion with automatic beats

Such observations show that the same ectopic centre, which produces automatic impulses, can also produce true extrasystoles with accurate coupling to the preceding beat. Similar observations were made by Rachmilewitz and Scherf in cases other than parasystole, namely, in cases of auricular fibrillation with coupled beats and in a case of sino-auricular block, and by Scherf and Schott (1932) in a case of complete A-V block with ventricular extrasystoles (For the relationship between automatic and extrasystolic impulse formation including the significance of the above observations, *see* chapter on " Mechanism ".)

Fig. 116 illustrates another combination between a parasystolic arrhythmia and extrasystoles It was obtained in a case of mitral stenosis with auricular flutter and fibrillation In this case a parasystole was found during five days' observation, during which the patient was given large doses of digitalis in order to convert auricular flutter into fibrillation Extrasystoles were recorded, having various shapes in the electrocardiogram and following only ventricular automatic beats, but never supraventricular ones (Scherf and Schott, 1951). The coupling of the extrasystoles was fairly constant and it could therefore be excluded that such beats were supraventricular ones with aberrant ventricular conduction Fig 116, top tracing, shows this arrhythmia during auricular flutter, the bottom tracing during auricular fibrillation No satisfactory explanation could be found for the observation, made in several cases, that extrasystoles occurred only after automatic ventricular beats. For some

* Closer inspection of their tracings shows that this phenomenon was only observed after ventricular [illegible] afterwards

tentative views on the underlying mechanism the reader is referred to the original paper (Scherf and Schott, 1951)

In conclusion it can be said that the occurrence of a parasystolic origin in some rather rare cases of ectopic arrhythmia has to be considered as established Not only does this conception offer the best explanation of such cases, but it also does not conflict in any way with accepted principles of cardiac physiology On the contrary, a more detailed analysis [illegible] were encountered when the originators of this idea made an attempt to explain by it the common variety of extrasystoles with accurate coupling. This having been generally abandoned, the distinction between a parasystolic mechanism, concerning an ectopic automatic rhythm, and extrasystoles in the strict sense of the term, being precipitated by the preceding beat, has furthered our understanding of the mechanism underlying both these groups of ectopic arrhythmias

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DISSOCIATION WITH INTERFERENCE

Definition and Relation to Parasystole

Dissociation with interference is a condition in which a faster atrio-ventricular (or, rarely,

ventricular) and a slower sino-auricular rhythm coexist and in which the slower sino-auricular rhythm at times interferes by conducted beats with the faster atrio-ventricular one

It follows that this arrhythmia falls within the range of pararrhythmias, the heart being stimulated by impulses originating in two independent centres As in parasystole, such an arrhythmia is only possible if the centre of the slower rhythm is protected from the faster impulses arising in the other one, otherwise the faster atrio-ventricular rhythm would dominate the whole heart, A-V rhythm resulting. The essential difference between parasystole and dissociation with interference is that, in the former, a slower ectopic rhythm interferes with a faster sino-auricular one, whereas in dissociation with interference it is the ectopic—A-V—rhythm which is the faster, and it is the normal pacemaker which produces the slower rhythm that interferes with the faster ectopic one In these two varieties of pararrhythmia, compared with one another, the rôles of relative rates between sino-auricular and ectopic rhythm are reversed and so are, for this reason, the rôles between the centre whose impulses interfere and that whose impulses are interfered with A further fundamental difference between parasystole and dissociation with interference is the periodic linking of both rhythms in the latter

Underlying Mechanism

As already stated, a slower sino-auricular rhythm can exist side-by-side with a faster A-V rhythm only if the slower centre is protectively blocked against the faster impulses of the other focus If this block is unidirectional and operates only in the retrograde direction from the A-V node towards the S-A node, whereas the spread of the excitation wave in the normal direction remains unimpaired, such sino-auricular impulses, which fall outside the refractory periods of the conducting system and of the ventricles, will yield a response from the ventricles How many of the sino-auricular impulses will thus become effective in the ventricles depends chiefly on the relation between the rates of the S-A and of the A-V rhythm, the A-V conduction time of the S-A impulses, and the length of the refractory period of the junctional tissues and of the ventricles Those sino-auricular impulses which reach the ventricles will temporarily interfere in a twofold manner with the A-V rhythm first of all, they will cause a " premature beat " of the ventricles within the otherwise regular sequence of the A-V ones, and secondly, the conducted impulses, while travelling through the junctional tissues, will interfere with the formation of impulses in the A-V node, so that the immature impulse there will be destroyed and impulse formation starts anew at the moment when the conducted impulse has left the A-V node With these conducted beats, and with these only, does the slower sino-auricular rhythm interfere with the faster A-V one, and it is with these beats that the two rhythms are linked

Experimental Observations

The occurrence of such an arrhythmia in certain experimental conditions was observed by Cushny as early as 1897 On the grounds of analysis of myocardiographic tracings of auricle and ventricle in dogs recorded during a certain stage of digitalis (strophanthin) intoxication he described it with remarkable clarity as follows

" Two independent rhythms may occur in the heart, and the contractions of each of the divisions concerned may be perfectly regular in force, rate and size This continues, however, only as long as the passage of impulses from the one to the other is blocked As soon as two rhythms occur without any hindrance to their passage from one division to the other, the contractions of each become irregular owing to the interference of the transmitted impulses with the contractions generated spontaneously in each division An impulse may

pass either to the ventricle from the auricle or in the reversed direction (McWilliam, Bayliss and Starling).

"Returning now to the tracings obtained after digitalis, we find that in the first stage we often have the same rhythm in auricle and ventricle throughout. In this case the rhythm is auricular, the inhibitory action slowing it, but not being strong enough to block the impulse passing to the ventricle As the action proceeds, the inhibition becomes weaker, or more probably the muscular action on the auricle overcomes the inhibitory and the rhythm becomes less slowed than immediately after the injection. The auricular rhythm is still, however, somewhat slower than normal, owing to the inhibition The muscular action is more marked on the ventricle and the inhibitory is less powerful. Accordingly, we find the irritability of the ventricle at last so great that the slow auricular rhythm is no longer sufficient to satisfy it and the ventricle takes up its own rhythm, and is therefore now set in motion by two sets of impulses, one generated in its own, the other derived from the auricular muscle. As long as the extraneous impulse reaches the ventricle during its refractory period it will have no effect, and if the two rhythms are nearly equal a number of impulses are therefore ineffective In this way the irregularity becomes periodic, the periods being longer at first when the rhythms are nearly equal, but becoming shorter as they diverge more from each other

"In the auricle the condition is similar, the same interference of the two rhythms occurring and the same periodic irregularity Occasionally, however, the auricle is fairly regular, while the ventricle is periodic This is because the passage of impulses from the auricle to the ventricle is much easier than in the opposite direction Thus we may have an interference occurring in the ventricle from the clashing of the auricular and ventricular rhythms while the ventricular impulses are unable to pass to the auricle, and the latter therefore beats perfectly regularly" (P 279)

These relationships were further clarified in the early days of electrocardiography. In 1910 Rothberger and Winterberg showed in experiments on dogs that, while atrio-ventricular rhythm was developing or subsiding, a transient stage exists during which the auricles are stimulated by the sinus node and the ventricles respond to A-V impulses. In a subsequent series of experiments the same authors obtained in 1912 electrocardiographic records demonstrating a dissociated cardiac action with occasional interference of conducted sino-auricular beats with an idioventricular rhythm (*see also* the reproduction of such a record in Rothberger, 1931, Fig 42)

In 1929, Scherf established that this arrhythmia occurred during a certain stage of aconitine intoxication Fig 117 provides an example It shows A-V rhythm periodically interfered with by conducted S-A impulses As a result of the injection of aconitine, the sino-auricular rate was slowed below the A-V one, the S-A rate being 50 and that of the A-V rhythm 67 per minute With great constancy one S-A impulse is conducted to the ventricles after every two A-V beats The R-R intervals between a conducted and the subsequent A-V beat (0 88) equalled those between two successive A-V beats, as would be expected (*see* below) (Aconitine also diminished the contractility of the auricles, as demonstrated by the absense of excursions of the mechanical record of the auricle Atropine restored immediately both normal rhythm and normal contractility) This arrhythmia was also found experimentally to occur as a result of emetine (Boyd and Scherf, unpublished experiments) and quinidine (Korns)

Clinical Observations

The first clinical case of this kind was described in 1906 by Wenckebach, who, on the grounds of mechanical records alone available at the time, gave it a different interpretation, but later agreed with the revised diagnosis. Wilson described in 1915 an instance of this arrhythmia, giving the tracings the interpretation, though not the name, which is now

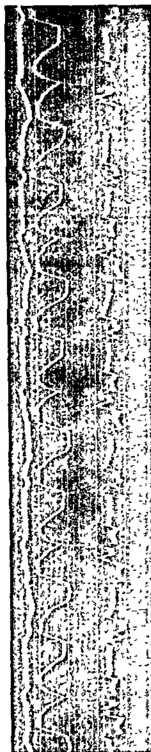


Fig 117.—Dissociation with interference experimentally produced in a dog by means of aconitine Tracings from above downward indicate suspension record of right auricle, that of right ventricle, electrocardiogram (ano-oesophageal lead), time base, 0 02 sec Note the absence of signs of contraction of the auricle, being due to high vagal tone The small waves in the auricular suspension record are due to transmitted ventricular contractions

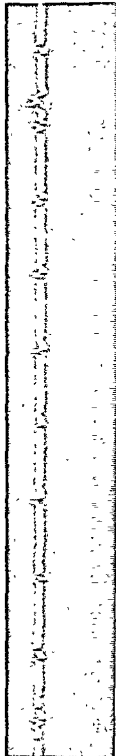


Fig 118.—Lead 2 Dissociation with interference, with slow rates of both centres

generally accepted Shortly afterwards cases with the correct interpretation were reported by White, and by Heard and Colwell. Whether the true mechanism was recognized by Lea in a paper published at that time (1915) seems doubtful.

That this condition was recognized as an arrhythmia *sui generis* is largely due to the extensive work of Mobitz (1923a), who called it " Interferenzdissoziation " and also showed that several other cases described earlier, but interpreted in various other ways, actually were cases of this kind (cases of Wenckebach, Weil, Taschenberg, Edens) In accordance with Wenckebach, Scherf proposed the term " Dissoziation mit Interferenz ", in preference to that of Mobitz (Scherf, 1926), best rendered in English as " dissociation with interference " A representative list of published cases of this arrhythmia is contained in the bibliography of this section Of the four cases reported by Stein and Bartlett, only Cases 2 and 4 are acceptable without reserve, their Case 3 is most probably an instance of this arrhythmia though the reproduced tracing is very indistinct.

Three cases of suprarenal tumour are on record in which dissociation with interference was recorded amongst arrhythmias observed during hypertensive crises. In this condition the arrhythmias are considered due to the adrenaline circulating in the blood (Burgess *et al*, Hegglin and Holzmann, Espersen and Jorgensen).

Fig 118 provides an example of this arrhythmia The record was obtained from a patient with hypertension and coronary sclerosis who had been treated with unknown doses of digitalis At the beginning of the tracing an automatic A-V beat is seen, followed by two conducted sino-auricular ones. The subsequent seven beats are A-V beats; the P waves, which occur in relation to these beats, gradually approach the ventricular complexes, then are fused with them and finally emerge after the initial complexes between the R-S-R' and T waves The ninth P wave of the record occurs sufficiently late after the initial ventricular complex of the preceding automatic A-V beat (the tenth of the record) to be conducted to the ventricles The tracing shows clearly that the first of the conducted beats gives rise to a premature contraction Subsequently the same cycle of slowly shifting rhythms with occasional conducted S-A beats repeated itself. In this instance the auricular rate was about 36 and the A-V rate 40 per minute This close proximity of the two rates resulted in a slow shift of the two rhythms, whereby most of the S-A impulses fell within the refractory period of the automatic A-V beats. It should be noted that the interval between the last conducted beat and the next automatic A-V beat equals that between two successive A-V beats This is to be expected in an uncomplicated case of this kind, since the conducted impulse destroys on its passage through the A-V node the immature impulse being formed there, at which moment the impulse formation in the A-V node starts afresh with the same rate as during the periods without interference It will be shown below that and why the time relations may be more complicated in some cases

That the A-V rhythm should be faster than the S-A one may be due to an abnormally slow S-A rhythm, for instance, due to a 2 . 1 sino-auricular block (presumably present in Fig 118), or to an abnormally fast A-V rhythm While a sharp distinction between these two varieties, as attempted by Dressler (1930), is unacceptable, Fig 119 may serve to illustrate this arrhythmia with faster rates It shows dissociation between a faster A-V rhythm of 85–88 with a slower S-A rhythm of 74–76 per minute The third and seventh S-A impulses are certainly, and the second most probably, conducted beats. Sometimes both the A-V and S-A rates vary; such variations tend to occur in the same direction and are attributed to variations in vagal tone (Scharf and Weiser, Scherf, 1926).

Since both the A-V and the conducted beats reach the ventricles through the normal paths it is to be expected that their ventricular complexes are the same, as is shown in Figs. 118 and 119. For two main reasons, however, the ventricular portions of the conducted beats may differ in shape from those of the automatic A-V beats First, this may be due to aberrant conduction in the ventricles of the conducted beats, owing to inadequate recovery



Fig 119 —Lead 2 Dissociation with interference, with faster rates of both centres

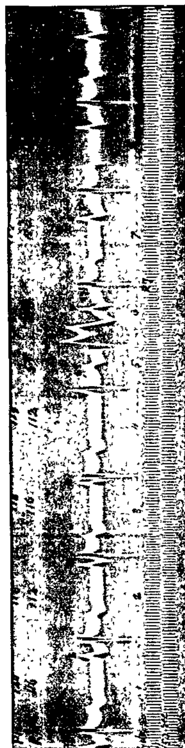


Fig 120 —Aberrant intraventricular conduction of a sinus beat in dissociation with interference From Schott, 1937b *Guy's Hosp Rep*

of the paths of conduction in the ventricles As in the case of auricular extrasystoles (*see* p 55) this tends to be the more pronounced the sooner after the preceding beat the premature impulse is to be conducted Fig. 120 provides an example It shows dissociation with interference between an A-V rhythm of 51 per minute (cycle length 1·16 seconds) and a very slightly slower S-A rhythm of 50–51 per minute (cycle length 1·17–1·20 seconds) The fifth sino-auricular impulse, which occurs at the very start of the fifth automatic A-V beat, is conducted to the ventricles with the lengthened A-V conduction time of 0 63 second and gives rise to a ventricular complex, the shape of which differs grossly from that of the A-V beats. The next S-A impulse is also conducted, but with the shorter P-R interval of 0 33 second, and its ventricular portion does not materially differ in form from that of the A-V beats It is obvious that, on superficial inspection, the first of these conducted beats may easily be misinterpreted as ventricular extrasystole (*see also* Burchell)

The second reason for a difference in shape in the ventricular portions of conducted and automatic A-V beats is dissociation with interference between an idioventricular centre and the normal S-A pacemaker Fig 121 shows such a case, demonstrating dissociation with interference between an idioventricular centre situated below the bifurcation of the bundle of His, and S-A rhythm With such a location of the centre of faster impulse formation the ventricular portions of its beats cannot resemble those of conducted beats The rate of the idioventricular rhythm was 94 per minute (cycle length 0 64 second), that of the S-A rhythm 85–88 per minute (cycle length 0·68–0·7 second) The long interval in the centre of the tracing, between the automatic beats before and after the sinus beats, measures 1 76 seconds, this is not a multiple of the automatic periods which indicates that there is no protection of the ectopic centre from the sinus beats In addition, this figure also shows the first variety of abnormally shaped ventricular complexes, namely, that of conducted beats due to aberrant conduction the seventh and eighth S-A impulses are conducted, the seventh with aberrant conduction

Special features regarding time relations

Reasons were given above for the statement that, in the uncomplicated case, the interval between the ventricular complexes of a conducted and that of the subsequent A-V automatic beat equals that between two successive automatic A-V ones. But this is not invariably the case, such intervals sometimes being found shorter, sometimes longer than the inter-automatic ones. The analysis of such differences has thrown some light on the underlying mechanism and is of physiological interest

Shortening of the inter-ventricular interval following a conducted beat may be found if more than one conducted beat follow in succession This tends to be particularly pronounced if the A-V conduction time of the first conducted beat is considerably longer than that of the second Such an instance is contained in Fig 120, in which the interval following the conducted beat P_5–R_6 is shortened to 0 88 from the usual 1·12–1·16 seconds inter-automatic interval of this case. During that time the rate of the S-A rhythm remained unchanged, and the shortening of the interval R_6–R_7 can be shown to be due to the difference in A-V conduction time between 0 63 second of the first and 0·33 of the second beat. But shortening of this interval is also observed if no second conducted impulse follows the first and this is of considerable physiological interest Fig 122 gives an example. It shows dissociation with interference between a faster A-V rhythm (R-R cycle length 0 86–1·00 second; rate 60–70 per minute) (disregarding the abnormally long cycle 17 for reasons given below), and a slower S-A rhythm (P-P cycle length 0 94–1·16 second, rate 52–63 per minute). Some S-A impulses are conducted and yield ventricular responses (cycles 1, 4, 10, 13) Cycles 2, 11 and 14, all of which follow conducted beats and are themselves certainly not terminated by a second conducted beat, are shortened to 0 66 and 0 68 second respectively. This phenomenon was first described by Scherf (1926) who established



FIG 121 —Dissociation with interference between sino-auricular and idioventricular rhythms

Cycle No 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Auricle 108 96 100 96 100 100 110 108 198 100 94 116 104 100 196

Node Bundle 44 50 48 46

Ventricle 56 66 86 56 84 90 88 100 92 52 68 90 52 68 92 94 110 100

FIG 122 —Dissociation with interference, with shortening of the interval following a conducted beat From SCHOTT, 1937b *Guy's Hosp Rep*

that it is due to delayed conduction of the conducted S-A beat in the bundle of His. As the delay takes place below the A-V node, impulse formation starts in the node, as in most cases of this arrhythmia, at the moment the conducted impulse has left the node; since, owing to the infra-nodal delay in conduction of the conducted impulse, the ventricular excitation of this beat occurs later in relation to the impulse's leaving the node, the subsequent interval is bound to be shortened The physiological importance of this observation lies in the fact that it forms one more proof of the occurrence of disturbances of conduction in the bundle of His (cp section on " Extrasystoles in A-V Rhythm and Return Extrasystoles ", p 102) This interpretation is also supported by the observation that in one case, showing this phenomenon, other signs of impaired conduction were present, namely, intra-auricular disturbances of conduction, lengthening of the A-V conduction time, and aberrant conduction in the ventricles (Schott, 1937a) Similar observations are contained in a paper by Luten and Jensen, though differently interpreted by the authors

Contrariwise, the interval following a conducted beat may be *lengthened* A small degree of such prolongation can be attributed to inhibition of A-V impulse formation as a result of the passage through the node of the conducted impulse In some cases, however, such intervals are far too long for this explanation to be acceptable Fig 123, taken from the same case as Fig. 120, demonstrates this phenomenon It shows dissociation with interference (rate of A-V rhythm 52–55 per minute; cycle length R-R 1 08–1·16 seconds, rate of S-A rhythm 46–54 per minute; cycle length P-P 1·12–1·30 seconds) The first two cycles show the P waves gradually approaching the automatic A-V complexes, the fourth P wave is fused with the last part of the ventricular complex of A-V beat No 4, and this beat is followed by an interval of 1·62 second, after which the heart beats in sinus rhythm for the next three beats The question poses itself why did no atrio-ventricular beat occur after the usual interval of 1·08–1 16 seconds? The same phenomenon occurred on two other occasions (cycles 9 and 14) Closer analysis of these and other records revealed that such abnormally long intervals were observed only if an auricular contraction fell *just* at the *end*, or *coincided* with the *beginning* of the automatic ventricular deflections. It could be shown that S-A impulses falling just in these phases were conducted to the ventricles, but failed to yield a response from the ventricles, as they were blocked in the lower parts of the conducting system The conducted impulse, while passing through the A-V node, there discharged the immature impulse, formation of the next A-V impulse starting again when the conducted impulse had left the node. However, before the next A-V impulse could become effective the next S-A impulse stimulated the ventricles as well as the auricles It will be observed that all three abnormally long intervals are, in fact, terminated by conducted beats. Thus, in these instances in which the impulse formation in the A-V node apparently suddenly fails to occur, the condition actually reveals itself as a further degree of impairment of conduction in the bundle of His, a sino-auricular impulse, though passing through the node, being blocked in the bundle. These relationships could be proved by calculation and were found to be accurate within 0 01–0 02 second (Schott, 1937b). The same mechanism is responsible for the abnormal length of cycle 17 in Fig 122, and for a similar phenomenon in Vedoya and Battini's case though interpreted by these authors as due to a sudden exit block (*see* preceding section on " Parasystole ", p 176). A similar explanation was put forward by Winternitz, who observed only one instance of this phenomenon which he attributed to a certain critical length of the R-P interval, intermediate between shorter ones not resulting in a conduction of the S-A impulse, and longer ones with the customary inverse relationship between R-P and the subsequent P-R intervals A similar view was expressed by Korth and Schrumpf (1936), but no time relations were given A further instance of this arrhythmia has recently been reported by Gentile (Case 1)

While, in such instances, the site of block has to be located in the main bundle, a case of

Cycle No. 1 2 3 4 5 6 7 8 9

Auricle 118 126 126 124 116 112 126 ?130 ?128

Node 32 28 28

Bundle

Ventricle 118 114 112 162 112 112 112 112 162

10 11 12 13 14 15 16 17

120 118 120 126 120 116 118 110

35 22 34 34 34

108 114 114 112 160 116 112

Fig 123 —Dissociation with interference, with lengthening of the interval following a conducted beat, owing to disturbances of conduction in the bundle of His The two strips are continuous From Schott, 1937 b *Guy's Hosp Rep*

dissociation with interference has been reported by Burchell in which disturbances of conduction of S-A impulses occurred in the right or the left bundle branch. Which of the two bundle branches failed to conduct depended on the interval between the P wave of the conducted beat and the R wave of the preceding A-V beat· with R-P intervals of 0·18–0 28 second left, with those of 0·30–0·39 second right bundle branch block configuration of the conducted beat was recorded The atrio-ventricular conduction time of beats with left bundle branch block was considerably longer than of those with right bundle branch block. Different recovery rates of the two bundle branches was assumed by way of a hypothetical explanation of this observation, and the possibility of a supernormal phase of recovery in conductivity of the left bundle branch block was considered

Whatever the reason in an individual case of dissociation with interference may be that causes the A-V rate to exceed that of the S-A pacemaker, the prerequisite for this kind of arrhythmia is that the rate of effective impulses produced by the A-V node exceeds that of the rate of S-A impulses being capable of being conducted at least as far as the A-V node Thus, halving of the effective S-A rate by 2 : 1 sino-auricular block is one of the various conditions that may give rise to this arrhythmia (*see* above Fig 118). The same holds good in cases of 2 1 A-V block, in which the rate of the automatic rhythm is faster than half the S-A rate (Dressler, 1929) In this connexion the observation is of interest that dissociation with interference occurred in a case of paroxysmal tachycardia with 2 . 1 A-V block At one stage, probably as a result of digitalis, dissociation with interference ensued when the A-V rate became a little faster than *half* the auricular rate (P-P intervals 0 28–0 3 second, auricular rate 200–214 per minute, R-R intervals 0 52–0·57 second, A-V rate 105–115 per minute) Owing to increasing disturbances of conduction below the A-V node of the conducted impulses, some of them failed to yield a ventricular contraction and abnormally long intervals in the ventricular rhythm resulted (Schott, 1946)

Dissociation with interference between a faster ectopic auricular rhythm and S-A rhythm *cannot be considered as established Mobitz's attempt (1923b) to explain in this way a case* reported and differently interpreted by Kaufmann and Rothberger (Case 1) is unconvincing and was rightly criticized by Schellong (1924)

Diagnosis

The recognition of this arrhythmia is only possible by graphic methods. On routine clinical examination it is bound to be mistaken for sinus rhythm with extrasystoles. a regular underlying rhythm is found which is occasionally disturbed by premature beats, and the conclusion would seem obvious that the regular rhythm is sinus rhythm and the prema- [illegible]

[illegible] electrocardiogram is available the main difficulty is to distinguish it from return extrasystoles (for a short summary of the main points *see* Herrmann and Ashman); this can only be achieved with certainty if longer records are taken An independent auricular rhythm is one of the essential features of dissociation with interference, and the diagnosis of this arrhythmia is supported if the P waves are upright in leads 1 and 2, or leads 1, 2 and 3 The shape of the P waves, in the presence of an independent auricular rhythm, also serves to [illegible] parasystole. Other points regard- [illegible] " Return Extrasystoles " (*q v*, [illegible] ctrocardiographically, particularly if only shorter records are used, and a typical record was misinterpreted as showing ventricular escape as recently as 1948 (Kirby)

Clinical Aspects

Conditions which are known to give rise to this arrhythmia are large doses of digitalis, infectious diseases (endocarditis, pneumonia), and impairment of the normal impulse formation in the sino-auricular node presumably due to impairment of its blood supply, in other cases no aetiological factor can be traced The chief and often sole complaint of the patient is palpitation which may be very troublesome; it is caused by the conducted beats Fainting and giddiness may occur in cases with marked sinus bradycardia The condition is often transient One unusual instance, in which this arrhythmia was recorded in a young child after scarlet fever and observed over several years, was reported by Schott (1951)

In many cases this arrhythmia does not require treatment If it can be assumed to result from digitalis treatment the drug should, of course, be temporarily discontinued In one case, in which no digitalis had been given, it was found that *small* doses of this drug (0 125 mg Digoxin, twice daily) abolished the arrhythmia and restored sinus bradycardia (Schott, 1937a)

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SUMMARY

Pararrhythmias are defined as a group of arrhythmias in which two (or rarely more) centres independently produce impulses which yield contractions of the whole heart or parts of the heart, without disturbances of conduction of the normal impulse being responsible for the arrhythmia

The prerequisite, which makes it possible for two independent rhythms to co-exist, is the protection of the centre with the lower rate of effective impulse formation against the intrusion of the stimuli produced by the faster centre Failing such a mechanism, which was termed protective (or entrance) block, the faster centre would dominate the rhythm of the whole heart.

Two main groups of pararrhythmias are distinguished (1) An automatic centre situated, with rare exceptions, in a ventricle, may produce impulses interfering with those of the normal pacemaker; this variety is called parasystole; (2) a faster atrio-ventricular rhythm

may co-exist with a slower sino-auricular one, the resulting arrhythmia being termed **dissociation with interference.**

Parasystole

Two varieties of this arrhythmia may be distinguished (a) parasystole with simple interference, and (b) parasystole with exit block

In parasystole with simple interference the impulses of a slower ectopic centre interfere with those of the faster sino-auricular node in such a way that the stimuli of either yield *ventricular contractions if they fall outside the refractory period of the preceding beat* The main criteria of this arrhythmia are the varying in length of the coupling of the ectopic beats to the preceding S-A beat; the simple mathematical relationship between the inter-ectopic intervals (which are defined as the intervals between consecutive ectopic beats separated by one or more S-A beats), the divisibility of the inter-ectopic intervals by the ectopic cycle length where the latter is directly measurable as the interval between two ectopic beats occurring in succession, the occurrence in the electrocardiogram of combination (fusion, summation) beats, intermediate in shape between those of beats produced by either centre alone, and being indicative of the simultaneous, or nearly simultaneous, activation of the heart by impulses originating from both centres Some qualifications and amplifications of these diagnostic criteria are discussed

A list of forty-nine cases is given in which this diagnosis can be considered to have been established, including eighteen personal hitherto unpublished instances It is pointed out that, as far as this small number makes it possible to draw any conclusions, this arrhythmia tends to occur in patients with structural heart disease

Four reported cases of parasystole with simple interference, in which the ectopic centre was situated in an auricle, are discussed and one personal observation is added.

One instance of ventricular parasystole with the ectopic centre located above the bifurcation of the bundle of His is discussed, as well as the experimental production of parasystole by means of veratrine

Parasystole with exit blocrk differs from the foregoing variety in that the rate of impulse formation in the ectopic centre is faster than that of the S-A pacemaker and that some of the ectopic impulses are prevented from becoming effective by a mechanism termed exit block Failing such exit block, an ectopic rhythm or ectopic tachycardia would result Several instances of this comparatively rare arrhythmia are given

Observations on *intermittent parasystole* are discussed, that is, a condition in which parasystole occuurs periodcally

The development of the conception of a parasystolic mechanism of some ectopic arrhythmias is discussed, with special reference to the pioneer work of Kaufmann and Rothberger It is pointed out that, contrary to the original contention of these authors, such a mechanism is unacceptable to explain the clinically common variety of extrasystoles with accurate coupling, but that their ideas have stimulated much thought in the analysis of clinical and experimental records of irregular heart action

The nature of the condition underlying protective and exit block is discussed, and experiments proving the existence of a protective mechanism are reviewed Regarding the possible mechanism of protective and exit block in clinical cases, the various views about its nature are discussed While most authors assume an anatomical substratum, located around, and in close proximity to, the ectopic centre, we believe that a diminished excitability of the ectopic, parasystolic centre in regard to the conducted impulses is the essential factor underlying such protection We therefore prefer the term " protective mechanism ", or " protection ", to " protective block "

The rare instances of transition, in the same case, of a parasystolic ectopic arrhythmia

into an extrasystolic arrhythmia with accurate coupling of the extrasystoles are reviewed The significance of such observations regarding automatic and extrasystolic impulse formation in ectopic centres is emphasized and reference made to the chapter on " Mechanism underlying the Origin of Extrasystoles" which is devoted to the discussion of this subject.

Dissociation with Interference

This is a condition in which a faster atrio-ventricular rhythm and a slower sino-auricular rhythm co-exist and in which the slower sino-auricular rhythm at times interferes by conducted beats with the faster atrio-ventricular one

As in parasystole, protection of the centre of slower impulse formation from the stimuli of the faster centre is a prerequisite, but, as distinct from parasystole, in dissociation with interference the ectopic—A-V—centre is the faster, and the normal pacemaker the slower centre

If an unidirectional block exists between the A-V and S-A node, operating only in the direction from the A-V to the S-A node, such sino-auricular impulses which fall outside the refractory period of the conducting system and of the ventricles will yield ventricular responses, and these conducted beats interfere with the otherwise regular A-V rhythm With these conducted beats, and with these only, are the two rhythms linked.

The conducted impulses give rise to " premature " beats and, since they destroy the immature impulse in the A-V node when passing through the node, the interval in the ventricular rhythm following a conducted beat is, in the uncomplicated case, equal to that between two successive A-V beats Since both the conducted and A-V beats reach the ventricles through the normal paths, the shape in the electrocardiogram of these two kinds of beats is, in the uncomplicated case, identical

Exceptions to this rule, both regarding lengths of intervals and shape of beats, are discussed, and it is pointed out that the closer analysis of these phenomena is fully in accordance with, and has thrown further light on, some principles of cardiac physiology Most of these exceptions could be shown to be due to disturbances of conduction of impulses in the bundle of His and/or in the ramifications of the conducting system in the ventricles

The reported clinical instances of this arrhythmia are reviewed and a representative list of published cases is contained in the bibliography of this section

The experimental conditions, in which this arrhythmia was observed, are reviewed

Clinically, the diagnosis can only be made by graphic methods since otherwise it is invariably mistaken for sinus rhythm with extrasystoles Electrocardiographically, it has to be distinguished from return extrasystoles and from auricular parasystole.

Large doses of digitalis and infectious diseases are the chief known precipitating factors

The condition tends to be transient and, in this event, no treatment is necessary In other cases temporary discontinuation of digitalis is indicated

CHAPTER IV

THE COUPLING OF EXTRASYSTOLES. BIGEMINAL RHYTHMS

Coupling is defined as the time interval between an ectopic beat and the beat preceding it All such ectopic beats are often termed "extrasystoles", but in our opinion this is undesirable for reasons fully discussed in this book Regarding the definition of coupling of ventricular extrasystoles, *see* also p 27, of auricular extrasystoles, p 48, for Lewis's terminology (Lewis, 1925) p. 27

ACCURATE AND VARYING COUPLING

According to their coupling, "extrasystoles" can be divided into two main groups

(1) those with accurate (constant, fixed) coupling in which the time interval between the "extrasystole" and the preceding beat is constant or varies within very narrow or systematic regular limits, and

(2) those with varying coupling in which variety "extrasystoles" occur in all phases of diastole

A sharp distinction between these two groups is justified on historical, experimental, clinical and theoretical grounds

The varying coupling which characterizes the above group (2) is the hallmark of an automatic ectopic centre of impulse formation co-existing with the normal pacemaker, the resulting arrhythmias—parasystole—are discussed in the chapter on pararrhythmias (*q v*) The present chapter is confined to the discussion of the above group (1) to which alone in our opinion the term extrasystoles in the strict sense of the word should be applied

BIGEMINAL AND TRIGEMINAL RHYTHMS

Extrasystoles with accurate coupling may occur singly, or after a longer or shorter series of beats of the dominant rhythm, or after each beat of the dominant rhythm In the last mentioned case the ensuing rhythm often is termed bigeminal rhythm or coupled beats Not infrequently this term is applied rather loosely and gives rise to confusion Used merely *in a descriptive way, it denotes a rhythm in which two beats occur within a comparatively* short interval which is preceded and succeeded by a longer pause While in the majority of such cases such rhythm is the result of an extrasystole following each beat of the dominant rhythm, this is by no means the only underlying mechanism as will be shown below For the sake of clarity we therefore recommend that, if this designation is used at all, it be qualified by adding the mechanism responsible for it, for example, bigeminal rhythm due to ventricular extrasystoles, bigeminal rhythm due to every third sinus impulse being blocked on their path to the ventricles, etc Some examples of bigeminal rhythm due to mechanisms other than extrasystoles are given later in this chapter

HISTORICAL

Supplementing what has been said in the chapter on "Historical Remarks", a few words about the development of our conception of bigeminal heart action and pulse may

not be amiss Traube was the first to observe, in 1862, what he called " zweispitzige Wellen " (bifid waves) in blood-pressure records, obtained after the injection of curare and bilateral vagotomy. Subsequently, in his paper on the effect of CO poisoning, he suggested the term *pulsus bigeminus* as superior to " zweispitzige Wellen " (Traube, 1865–66) In 1872 he encountered in pulse tracings of patients what he called a variation of the *pulsus bigeminus*, which he designated *pulsus alternans*, namely "a succession of high and low pulses, in such a manner that a low pulse regularly follows a high pulse and this low pulse is separated from the ensuing high pulse by a shorter pause than that between it and the preceding high pulse " (Traube, 1872, quoted from *Cardiac Classics*, p 591) While Traube succeeded in differentiating the dicrotic pulse from *pulsus bigeminus* and *alternans*, a confusion between the two latter had been started which for a considerable time was to obscure the analysis and particularly the prognosis of this group of arrhythmias An added source of confusion about the significance of " bigeminal heart action " was due to Wenckebach's contention, which he maintained for several years (1903, 1906), that true bigeminy should only be assumed in cases in which the two beats of the twin contraction were accurately coupled and of an identical nature, and that this form of arrhythmia had no connexion with extrasystoles This view was soon contested by Hering (1904, a, b) (who attacked Wenckebach in language leaving little doubt about the strength of his convictions and the intensity of his emotions, 1904b) and had to be abandoned when it was established by Lewis (1910) that the two beats of the pair originated in different foci

A different kind of terminological confusion has arisen more recently in regard to the word trigeminus Wenckebach (1914) defined tri-, quadri- and polygeminy as arrhythmias in which two, three, or more extrasystoles, respectively, follow one another, and many authors before and after him have used these terms in this way Of late, however, the designation trigeminus has been applied to arrhythmias in which one extrasystole followed two normal beats Occasionally the same term has even been applied by the same author

is in accordance with the historical development—which originated from Traube's use of the term *pulsus bigeminus* (*see* above, and also section on "Ventricular Extrasystoles", p. 33—it is clearly undesirable to use the same word to describe two totally different kinds of arrhythmia Kisch who, in 1945, devoted a special study to this question of terminology, and to whose paper the reader is referred for particulars about the various ways in which various

were originally suggested

EXPERIMENTAL

In contradistinction to the great frequency with which extrasystoles with constant coup-

with the

the rabbit by clamping of the carotids after sensitization of the animal with barium (Schott, 1934) (*See also* chapter on " Nervous System ", p. 225) Of these, the first is the one that has been most extensively studied Fig 124 provides an illustration. Fig 124a was recorded from a dog after the injection of such small doses of aconitine that no effects

could be traced either in the mechanical (suspension) records of the right auricle and ventricle, or in the electrocardiogram which shows sinus rhythm Stimulation of the right vagus in the neck immediately produced ventricular bigeminy with extrasystoles of constant shape and constant coupling following each sinus beat (Fig 124b).

It will be shown elsewhere in this book (chapter on " Mechanism ") that extrasystoles in the strict sense of this term originate in a circumscribed focus where they are precipitated by the preceding beat The behaviour of the coupling proved to depend on the path which the impulse of the initiating beat had to traverse in order to reach the centre of extrasystolic impulse formation Fig. 125 is taken from one of these experiments (Scherf, 1930) Fig. 125a shows a continuous bigeminal rhythm in a dog, following injection of aconitine. Each sinus beat was followed by an extrasystole which originated in the left ventricle; the extrasystoles had the same shape and constant coupling of 0·225 second When the right bundle branch was temporarily damaged by means of pressure with the back of a small knife, the ventricular complexes of the sinus beats assumed the shape seen in bundle branch block

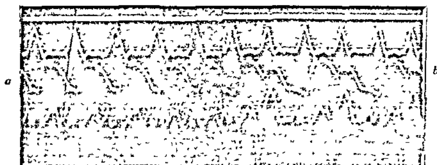


FIG 124 —From an experiment on a dog Tracings from above downward are suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base 0 02 second *a* After injection of

(widened QRS complexes, *see* Fig 125b) The coupling of the extrasystoles remained un-

shape of the extrasystoles remaining the same (Fig 125c) This lengthening must be attributed to the fact that, after the left bundle branch had been cut, the sinus impulses could reach the extrasystolic centre only via the longer path of right bundle branch and right ventricle. Subsequently the right bundle branch was also severed and complete A-V block resulted The idioventricular automatic beats originated in either the right or the left ventricle, each being followed by a left-ventricular extrasystole, as before Again, the length of coupling of the extrasystoles depended on the length of the path which the initiating impulse had to traverse in order to reach the extrasystolic centre, that is, depended on the

view that extrasystoles originate in a circumscribed focus

FIG 125.—From an experiment on a dog Recording as in the preceding figure *a* Ventricular bigeminy following injection of aconitine *b* After temporary damage to right bundle branch *c* After severing of left bundle branch *d* After severing of both bundles For further explanation, see text From SCHERF, 1930 *Z ges exp Med*

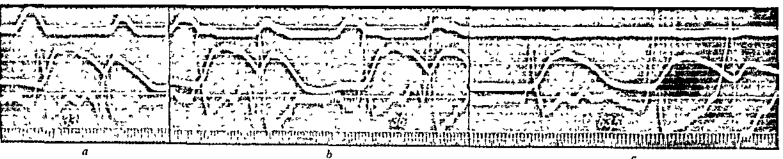


FIG 126.—From an experiment on a dog Recording as in the last two preceding figures Gradual lengthening of the coupling caused by quinine From SCHERF and SIEDEK *Z ges exp Med*

The length of coupling of extrasystoles is also affected by certain drugs. Regarding extrasystoles produced by aconitine their coupling may increase at the end of a series of extrasystoles just before they disappear (Scherf, 1929a). Other drugs having a similar effect on extrasystoles produced in this way are atropine (Scherf, 1929b) and quinine (Scherf and Siedek, 1935). Fig. 126 provides an example of the latter. In a dog, ventricular bigeminy had been produced by aconitine, the extrasystoles having the constant coupling of 0·23 second. Following the injection of the unusually large dose of 0 5 gramme of quinine bisulphate in a 20 per cent. solution, marked changes occurred in the shape of the extrasystoles and their coupling increased to 0·29 second (not shown). A second injection of the same dose of quinine caused a further lengthening of the coupling to 0·33 second (Fig. 126a) and subsequently to 0 36 second (Fig 126b) After a further injection of 0 2 gramme quinine the coupling attained 0 635 second (Fig 126c)

CLINICAL OBSERVATIONS

In clinical experience extrasystoles with constant coupling are far commoner than those with varying one. Amongst sixty cases with extrasystoles (fifty-one ventricular, nine auricular in origin) followed by a compensatory pause, constant coupling was found in 91·6 per cent. (Schellong, 1924) According to our experience this percentage is probably even higher In this variety of extrasystoles the coupling remains remarkably constant even with pronounced changes in the rate of the S-A rhythm (Wenckebach and Winterberg, 1927). If the cardiac rate increases considerably as the result of atropine the coupling remains constant (Hering, 1904a, pulse tracings only), and Samet observed a patient in whom the coupling remained unchanged 0 44–0 46 second during S-A rhythm and during an attack of auricular fibrillation Frey (1918) found such variations not to exceed 0·06 second in seventeen out of twenty cases Also in extrasystoles caused by digitalis, which are characterized by almost continual changes in shape, the coupling was found to vary only by 0 02 second in eleven out of fifteen cases and (with one exception) by not more than 0 03–0 04 second in the remaining ones (Scherf, 1931, 1932)

If different cases are compared it is found that, on the whole, the range of coupling of extrasystoles is comparatively small, extending from about 0 35 to 0·6 second. This is also true for digitalis extrasystoles in fifteen cases in which the coupling was accurately measured it ranged from 0 35 to 0 56 second and seven amongst these showed figures of 0·35–0 45 second (Scherf, 1931)

In rare cases this range is considerably exceeded on either end. Thus Fig 127 shows auricular fibrillation with extrasystoles occurring with the exceptionally long coupling of 1 12 seconds In such a case a re-entry mechanism to account for the extrasystoles is clearly impossible (*see* chapter on "Mechanism") The other extreme is illustrated by Fig 128, obtained from a patient with coronary sclerosis, in which extrasystoles are seen with a coupling of only 0 26 second, occurring before the T wave of the preceding beat had been fully inscribed From observations like these it was deduced by some that the extrasystolic stimulus must be a strong one, for a critical discussion of this view *see* section on "Intensity of Stimulus", p 367

If the coupling of ventricular extrasystoles is comparatively long in relation to the rate of the underlying rhythm, that is, if the extrasystoles occur very late in diastole, after the P wave of the subsequent normal beat is fully inscribed, they are scarcely premature or not

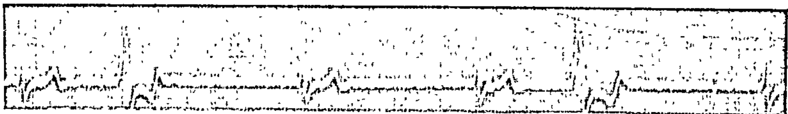


Fig 127 —Auricular fibrillation with ventricular extrasystoles showing the unusually long coupling of 1·12 seconds

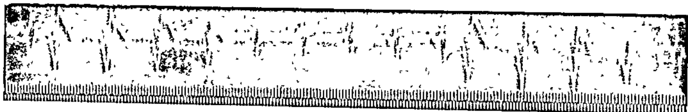


Fig 128 —Series of ventricular extrasystoles the first of which shows the unusually short coupling of 0 26 seconds

extrasystoles Owing to slight variations in the rate of the sinus rhythm the extrasystoles occur so late that, in some parts of the tracings, the coupling measures as much as the R-R intervals between two sinus beats—0 52 second—so that in this case the extrasystoles can hardly be said to be premature. Extrasystoles of this timing are formed at a time when the next normal impulse spreads over the ventricles (Calandre, 1920) They may easily be confused with sinus beats with aberrant conduction in the ventricles

Periodical Spontaneous Changes in the Length of Coupling

In addition to the common variety of extrasystoles with constant, and the infrequent one of ectopic beats occurring with varying coupling, periodical spontaneous changes of coupling of extrasystoles are seen in rare instances

One variety is a gradual lengthening of the coupling in successive extrasystoles until one is " dropped " and the cycle starts anew Three instances of this have been reported In

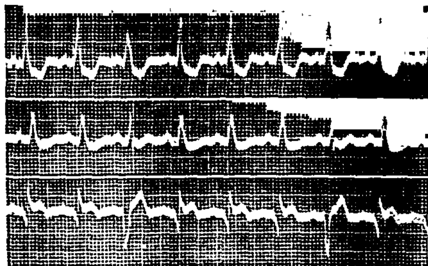


Fig 129—The three standard leads Ventricular extrasystoles occurring so late in diastole that they are not premature

by the assumption of disturbances of conduction of the normal impulse on its way to the centre of ectopic impulse formation This interpretation was criticized by Goldenberg and Scherf who published in the following year an instance of a similar, though more complicated, arrhythmia Whereas in Zander's case the arrhythmia was found on only one occasion—subsequent tracings showing either sinus rhythm or ventricular extrasystoles with fixed coupling of 0 48–0 50 second—Goldenberg and Scherf recorded ventricular extrasystoles with periodically changing coupling on numerous occasions Fig 130, top record, reproduces one of their tracings The first two beats are sinus beats, the second to fifth

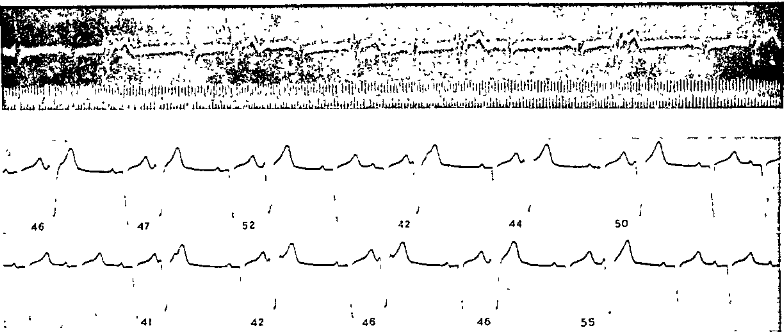


Fig 130.—Two instances of gradual lengthening of the coupling with dropping of extrasystoles The top record is from Goldenberg and Scherf *Wien Arch inn Med* The two strips of the bottom record are continuous, lead V-1

sinus beats are each followed by a ventricular extrasystole the coupling of which increases from 0 48 to 0 6 second After the next sinus beat no extrasystole occurs. Subsequently the same phenomenon is seen to start again, the coupling of the last two extrasystoles increasing from 0 48 to 0 52 second In this case a coupling of 0 80 was observed on one occasion At other times, however, the opposite behaviour was recorded, namely decrease in length of successive couplings; two extrasystoles occurring in succession and having the same shape were also seen, whereby the interval between the two ectopic beats was usually shorter than the coupling of the first extrasystole of the group. While Goldenberg and Scherf found it impossible to determine the underlying mechanism with any degree of certainty on the ground of their observations in only one such unusual instance, they were able to show that their case cannot be explained by assuming disturbances of conduction and that disturbances of impulse formation was a more likely tentative explanation The fact that the shortening of successive couplings tended to be observed at a time when extrasystoles had been absent for some considerable period pointed to some possible analogy with the

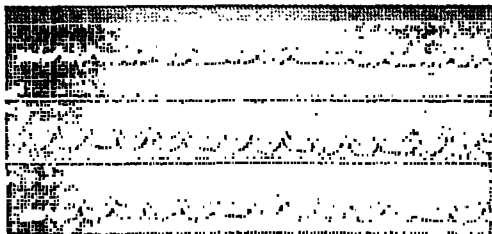


FIG 131 —Auricular bigeminy with alternation in the length of the coupling

" rhythm of development ", namely the gradual quickening of the idioventricular rate after severing the A-V bundle in the frog (Gaskell, 1883) A somewhat similar case has been observed by Mack and Langendorf [illegible]

from 0 46 to 0 52 second after which two sinus beats occur in succession, one extrasystole being "dropped" The same phenomenon occurred subsequently, the coupling gradually increasing from 0 42 to 0·50 after which five sinus beats occurred without any extrasystole The bottom strip shows the same phenomenon, namely a gradual increase of the coupling from 0 41 to 0 55 second, with subsequent " dropping " of the premature beats.

Anoth[illegible] nation [illegible] shows [illegible] intervals between the beginning of the P waves of the extrasystoles and that of the preceding QRS complex alternating between 0·28 and about 0 20 second (Owing to the superposition

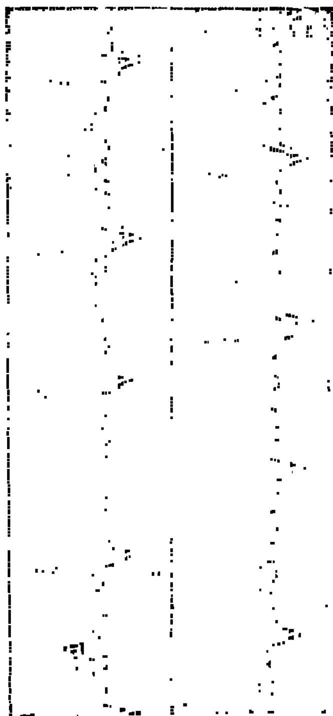


FIG 132 —Lead 3 The two strips are continuous Ventricular extrasystoles after every two sinus beats with alternation in the length of the coupling.

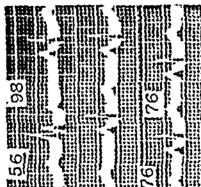


FIG 133 —Lead 2 The three strips are continuous Ventricular extrasystoles with varying coupling, also fusion beats, without any evidence of parasystole



FIG 134 —Lead 2 Sinus (?paroxysmal auricular) tachycardia, left bundle branch block with 2 : 1 and 3 : 2 A-V block From SCHOTT, 1951. *Trans med Soc Lond.*

of the P waves of alternate extrasystoles upon the T waves of the preceding beats accurate measurement is impossible.) The more premature series of extrasystoles shows abnormal ventricular deflections owing to aberrant intraventricular conduction.

An example of alternating coupling of *ventricular* extrasystoles is provided by Fig. 132, recorded in a woman of seventy-three a few weeks after an attack of coronary occlusion One ventricular extrasystole occurred after every two sinus beats and their coupling alternated between 0·38–0·40 and 0 56–0 58 second.

Occasionally extrasystolic arrhythmias with varying coupling of the ectopic beats and even with fusion beats are recorded in which a parasystolic mechanism cannot be established (Fig 133).

Bigeminal Heart Action due to Arrhythmias other than Extrasystoles

When a sequence of two heart beats followed by a longer interval is found on auscultation, the condition is almost invariably diagnosed as "extrasystoles", that is, one beat of

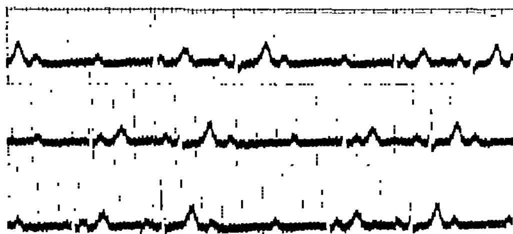


FIG 135 —All strips lead 2 Partial A-V block with idioventricular escaped beats

the dominant rhythm followed by an extrasystole, this couple being followed by a post-extrasystolic pause In the majority of cases this clinical diagnosis will be correct, and confirmed if an electrocardiogram is taken But in quite a proportion of such instances the underlying mechanism is different and, from a clinical point of view, a clear recognition of the arrhythmia is of great importance

Some arrhythmias invariably giving the clinical impression of extrasystoles are fully discussed elsewhere in this book, for example, dissociation with interference. Others too can be distinguished by an electrocardiogram at a glance, for instance, second grade heart block in which every third beat is dropped, or 2 : 1 block with occasional or alternating 1 1 conduction (*see* Fig. 134) In others again, however, detailed analysis of an electrocardiogram is necessary for an accurate diagnosis to be made; Figs 135, 136 and 137 provide examples

The tracing reproduced in Fig. 135 was obtained in a seventy-one-year-old man with attacks of momentary unsteadiness due to advanced arteriosclerosis The record shows partial heart block; after two blocked P waves an automatic ventricular beat (ventricular escape) occurred which was followed by a conducted S-A beat with normal conduction time

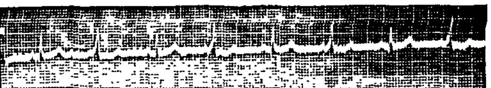


FIG. 136.—Lead I. Pre-excitation syndrome with alternation between normal and abnormal conduction.

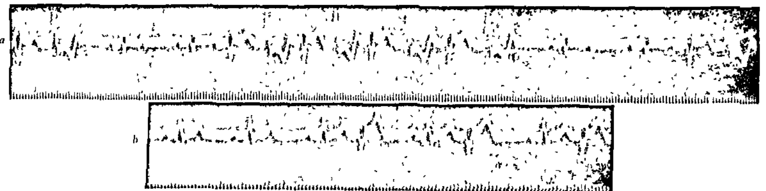


FIG. 137.—From the same patient recorded on different days. Sinus tachycardia with disturbances of A-V and intraventricular conduction simulating ventricular extrasystoles and ventricular tachycardia. For further explanation, see text. From SCHERF and KISCH, 1939, *Bull. N.Y. med. Coll.*

(P-R· 0 16 second). Analysis of longer continuous records supported the interpretation that the conduction of the beats following the idioventricular ones was due to the presence of a supernormal phase of recovery The bigeminal heart action was due to the persistence, over long periods, of two beats occurring in comparatively quick succession, such couples being preceded and succeeded by longer intervals These longer intervals were due to partial heart block, and what gave the clinical impression of an extrasystole actually was a conducted beat succeeding an idioventricular one at a short interval (Schott, 1949).

Fig. 136, at a casual inspection, conveys the impression of an extrasystole occurring very late after each normal beat. the ventricular complexes of the abnormal beats are slightly premature and, as the P waves of these beats are of the same shape as those of the sinus beats and do not occur prematurely, such a diagnosis would appear justified, that is, of the same condition as shown in Fig 129. Closer inspection reveals, however, that the P-R intervals of the abnormal beats are very short (0 08 second as compared with the 0 12 second of the normal ones) and that the upstroke of the R waves of the abnormal beats are grossly slurred whereas the remaining portions of the QRS complexes are of normal shape These features suggest that every second beat represents the Wolff-Parkinson-White (pre-excitation) syndrome which is now commonly attributed to activation of the ventricles through an abnormal pathway, often called the bundle of Kent (Holzmann and Scherf, 1932, Wolferth and Wood, 1933, a short summary of this condition is contained in a paper by Schott, 1947) In this present case a diagnosis could not be made with certainty either from the reproduced lead or from the other leads recorded at the time, but this was possible by tracings taken after exercise or after inhalation of amyl nitrite. whereas extrasystoles tend to disappear after the former and to become more numerous after the latter, in the present case the rate increased without any other changes in the form of the electrocardiogram

An entirely different mechanism producing bigeminal heart action, which again could easily be misinterpreted as due to extrasystoles, is shown in Fig 137 In this case bigeminal groups were recorded as well as what appeared to be short series of tachycardia with alternating form of the QRS complexes (Fig 137a) Measurement reveals, however, that the underlying rhythm is a rather fast sinus rhythm and that at times every second auricular impulse is blocked During periods of 1 1 conduction grossly abnormal ventricular deflections with alternating shape occurred, and what gave the impression of extrasystoles actually were supraventricular beats with aberrant intraventricular conduction

Fig 137b, recorded from the same patient on a different day, can easily be confused with a ventricular bigeminy The first impression is that of sinus rhythm, with a ventricular extrasystole following each sinus beat in the second half of the tracing Measurement of the intervals between successive beats reveals at once, however, that this cannot be the correct explanation since the intervals after the " extrasystoles " are far shorter than compensatory. On the other hand, the interval between a normal beat and one having an abnormal ventricular complex is found to be exactly half of the cycle length between two normal beats, while that between the abnormal and the following normal one equals that between two normal complexes The correct interpretation is sinus tachycardia of about 120 with 2 . 1 block at the beginning of the tracing whereby every second P wave is buried in the T wave of the preceding beat Subsequently the rhythm changed into 3 2 block; the first beat of each group shows normal QRS complexes, the second is aberrantly conducted in the ventricles, and the third one is blocked (Scherf and Kisch, 1939)

In accordance with experimental findings, discussed earlier in this chapter, lengthening of the coupling of extrasystoles by quinine has also been reported in clinical observations. Fig 138 provides an example. It was recorded from a patient who was under observation for several years and on numerous occasions had extrasystoles and short attacks of ventricular tachycardia with alternation of the ventricular complexes On one occasion such an

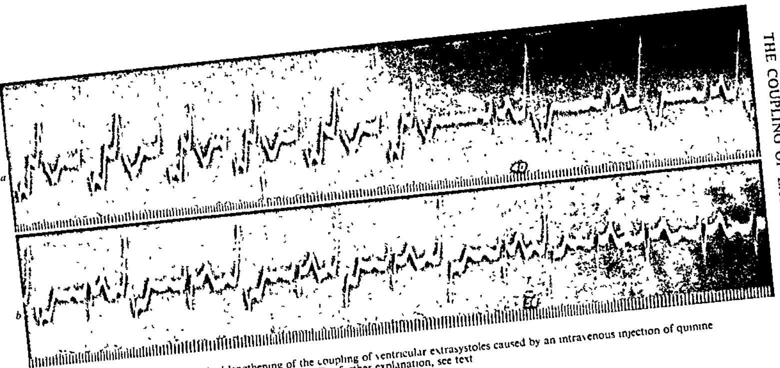


Fig 138 —Lead 3 Gradual lengthening of the coupling of ventricular extrasystoles caused by an intravenous injection of quinine
For further explanation, see text

attack stopped 27 seconds after the intravenous injection of 0·25 gramme of quinine and was replaced by bigeminal heart action in which one extrasystole with constant shape and increasing coupling followed each sinus beat (Fig. 138a). In the first bigeminal group the coupling measures 0·40 second, then gradually increases and with the last extrasystole attains 0·56 second — 52 seconds after the beginning of the quinine injection (Fig. 138b). About 20 minutes later the effect of quinine had subsided and the former tachycardia with alternating ventricular complexes re-appeared (Scherf and Winterberg). Lengthening of the coupling of extrasystoles by quinine was also reported by Scott (1922), Scherf (1924) and McGuire and Rosenberger (1931). It is also occasionally observed after carotid sinus pressure.

SUMMARY

Coupling is defined as the time interval between an "extrasystole" and the beat preceding it.

According to their coupling, "extrasystoles" can be divided into two main groups

(1) with accurate (constant, fixed) coupling,

(2) with varying coupling.

The present chapter is confined to the discussion of the above group (1), to which alone, in our opinion, the term extrasystole in the strict sense of the word should be applied.

If one extrasystole with constant coupling follows each beat of the dominant rhythm the resulting arrhythmia is often termed bigeminal heart action or coupled beats. While in the majority of observations bigeminal heart action is caused by this mechanism, this is by no means invariably the case. It is recommended that the term "bigeminal heart action" be qualified by adding the description of the mechanism responsible for it. The historical development of our conceptions of bigeminal heart action is briefly reviewed. Reasons are given for the recommendation that the term "trigeminus" should only be used to describe an arrhythmia in which two extrasystoles follow one beat of the dominant rhythm. While extrasystoles with constant coupling are very common in clinical experience, they are very difficult to elicit in experimental work. The methods known to produce this arrhythmia experimentally and some relevant experimental observations are discussed. The length of the coupling of extrasystoles proved to depend *inter alia* on the length of the path which the impulse of the initiating beat had to traverse in order to reach the centre of extrasystolic impulse formation. Regarding clinical observations it is pointed out that constant coupling is found in well over 90 per cent of cases with extrasystoles. The great constancy of the coupling in the individual case is emphasized. It is maintained even if the dominant rhythm shows large variations in rate. *On the whole, the range of coupling is comparatively small*, extending from about 0·35 to about 0·6 second. Observations regarding cases with unusually long or short, or periodically varying coupling are described. Some examples of bigeminal heart action due to arrhythmias other than extrasystoles are given. The effect upon the length of coupling of certain drugs, as found experimentally and clinically, is briefly reviewed.

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CHAPTER V

ALTERNANS

INTRODUCTORY REMARKS AND DEFINITION

In considering the phenomenon of alternation, its manifestation in the heart as well as in the pulse has to be taken into account Regarding the pulse, *pulsus alternans* consists in a regular alternation between a larger and a smaller pulse whereby the smaller pulse occurs either midway between two larger ones, or slightly later than midway. In such cases, the cardiac action is regular normal S-A rhythm, and the alternation in the strength of the pulse is due, not to any arrhythmia or allorhythmia, but to an alternating change in the force of the cardiac contraction. According to Kisch (1932). " Cardiac alternans may be defined as a regular alternation in the bio-energetic processes in the heart, occurring in two consecutive beats, and not being due to the regular alternation in the time sequence of the individual contractions " (our translation). With certain reservations, which Kisch pointed out, Gravier's (1914) definition can be said to state the essence of the phenomenon as " alternance de force des contractions, sans altération de leur rythme ".

It could thus be argued that a discussion of the alternating pulse is out of place in a book devoted to certain arrhythmias We have included it for two reasons

The first is historical. As is pointed out in the historical remarks and in the chapter on " Coupling ", the alternating pulse was first described by Traube, who clearly recognized its characteristics, including the correct time relations between large and small pulses. In spite of the accuracy of his observations he considered it as one variety of the bigeminal pulse and thereby created a confusion, affecting diagnosis as well as prognosis, which was to obscure the true significance of extrasystolic bigeminy and alternation for a long time to come This may well be one reason why a discussion of the *pulsus alternans* was included in the classical monographs of Lewis (1925) and of Wenckebach and Winterberg (1927) A second and more important reason for our including this phenomenon is the fact that extrasystoles greatly enhance alternation of the pulse

It has been pointed out above that, in instances of *pulsus alternans*, the rhythm of the heart is normal regular S-A rhythm. While this is correct for the vast majority of cases, it should be qualified by adding that some rare exceptions exist in which bigeminal rhythm due to extrasystoles occurring very late in diastole (*see* below), and certain varieties of heart block occasionally give rise to *pulsus alternans* (Lewis, 1925).

DIAGNOSIS

This is often made by the palpating finger [illegible]

[illegible] quently, over a range of pressures varying in different patients, the alternation in the intensity of the arterial sounds is very obvious. In rare cases, in which the weaker pulses are very small, only every other pulse is felt at the wrist

The differentiation between *pulsus alternans* and *pulsus bigeminus* is discussed below in this chapter.

INCIDENCE

The phenomenon is common, if searched for (Gravier, Poumailloux). It was found in seventy-one out of three hundred pulse tracings recorded from patients with cardiovascular disease, and in 33 per cent of patients with congestive heart failure (White).

EXPERIMENTAL INVESTIGATIONS

Experimentally, alternating pulse is readily observed with increased arterial resistance (Straub), fatigue (Hofmann), or after coronary ligation (Kisch, 1921). Various substances are known to precipitate it, for example digitalis, aconitine (Cushny) and veratrine

EXTRASYSTOLES AND ALTERNATING PULSE

The precipitation by extrasystoles of an alternating pulse has been extensively studied (Gaskell, Langendorff, Woodworth, Volhard Rihl (1906a, b), Mackenzie, Tabora) In the series of seventy-one cases of White, mentioned above, alternating pulse was seen only after



FIG 139 —Radial pulse tracing electrocardiogram and time base (0 04 second) Pulsus alternans precipitated by an auricular extrasystole From SCHERF and BOYD, *Cardiovascular Diseases* Heinemann, London

extrasystoles in fifty-five instances Sometimes alternation precipitated by an extrasystole may last for as many as forty pulses According to some authors, an alternating pulse may not appear immediately, but only after a few pulses following an extrasystole The beginning of alternation just before an extrasystole, as reported by Windle (1911) and by Rosenthal seems to us a coincidence A diminished degree of alternation following an extrasystole [illegible]

the heart, but also on its rate and on the number of extrasystoles In some patients with frequent extrasystoles a continual alternans seems to exist because the extrasystoles maintain it for long periods. In cases showing alternation during regular normal sinus rhythm extrasystoles accentuate the alternation

Arrhythmias other than extrasystoles may have a similar effect, for instance dropped beats (Hering, 1908) It seems that it is not the extracontraction, but the irregularity of rhythm which elicits the alternation.

Fig. 139 was obtained from a patient with coronary sclerosis and auricular extrasystoles. The abnormal T waves indicate myocardial damage. In the radial pulse tracing the first post-extrasystolic pulse is very high The next pulse is smaller and regular alternation in the height of the pulse waves can be recognized in the subsequent beats.

Just as in Fig 139, the first post-extrasystolic pulse wave is always higher, whatever the [illegible] (*see also* p 363) For this [illegible] (The only dissi- [illegible] in be disregarded, since in the absence of an electrocardiogram the nature of the post-extrasystolic beat, particularly *its mode of spread*, cannot be determined)

AURICULAR ALTERNANS

Auricular alternation manifests itself by alternation in the height of the (auricular) *a* waves in the phlebogram Such instances were described by Lewis (1911) and by Pezzi and Donzelot (1913) Doubts regarding the diagnosis were expressed by Gravier, but Pezzi and Donzelot reported in 1921 an observation in a patient with nephritis and azotemia in whom auricular alternans followed auricular, but not ventricular extrasystoles

CARDIAC PHENOMENA

Pulsus alternans is often associated with cardiac alternans In such cases alternation of the force of cardiac contraction can be felt on palpation, or recorded in a (mechanical) cardiogram Also, the second aortic sound may alternate in intensity and the alternating strength of contractions can be recorded in a kymogram

As distinct from such alternation in the dynamic force of the cardiac contraction, *electrical alternans* is defined as alternation in height or form of some or of all waves of the ventricular complex of the electrocardiogram Such electrical alternans is often found in otherwise normal people during an attack of paroxysmal tachycardia, in rare instances the P waves show electrical alternans (*see* Fig. 140) Disturbances of conduction are another frequent cause Recently, the various mechanisms underlying electrical alternation were experimentally studied and classified on electrophysiological grounds by Lepeschkin What is relevant in the context of this book is that the electrical alternans may or may not be associated with mechanical alternation

DIFFERENTIATION BETWEEN PULSUS BIGEMINUS AND PULSUS ALTERNANS

[illegible] due to premature beats or associated with normal rhythm

The diagnosis from radial pulse tracings alone is possible in a considerable proportion of cases, but often fraught with difficulties The main diagnostic criterion is that, in the [illegible]

the weaker contraction, which has to overcome the higher diastolic pressure in the aorta (and the whole arterial system) resulting from the preceding stronger contraction (Volhard) It might thus appear that the difference in these two pulse forms should make it possible easily to diagnose the underlying mechanism The conditions are, however, greatly complicated by the fact that in extrasystoles, too, the presphygmic period is lengthened. Measured as the time interval between the beginning of systole, as recorded in the mechanical cardiogram, and the beginning of the upstroke in the radial pulse tracing, it may amount to as much as 0 04 second (Hering, 1902). This is largely due to the altered haemodynamics in ectopic beats, in particular the lengthening of systole (*see* p 355) Therefore, if extrasystoles occur late in diastole, their pulse may well be not premature in the radial tracing.



FIG 140.—From a healthy woman of 35 Electrical alternans of the P waves during an attack of paroxysmal tachycardia

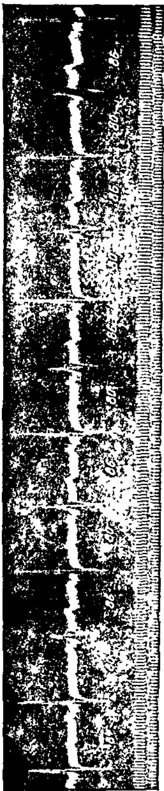


FIG 141.—Ventricular extrasystoles occurring late in diastole simulating electrical alternans Time base 0 04 second

Fig 141 provides an example of this kind of extrasystoles. It shows regular alternation between normal and slightly abnormal ventricular complexes, whereby the outstanding difference is the alternation in the height of the various waves of the ventricular complexes Since both types are always preceded by P waves at normal intervals, casual inspection would indicate the presence of sinus rhythm, with electrical alternans. Measurement reveals, however, that the smaller and abnormally looking complexes occur after an interval of 0·80, while the following cycle length measures 0 86 second. The abnormal beats are therefore ventricular extrasystoles occurring very late in diastole, at a time when the next normal sinus beat was about to be due That this diagnosis is the correct one could be proved by other tracings of this patient in which the extrasystoles occurred earlier in diastole and the diagnosis could thus easily be made. It is obvious that, in such instances, a radial pulse tracing would show the smaller pulse of the extrasystole to occur so late that the time relations would be indistinguishable from those produced by alternation with regular sinus rhythm. (*See also* Fig. 129 on p. 199)

Moreover, a slight delay in the small pulse due to alternans may easily be missed in the radial tracing

If follows that the differential diagnosis, from radial tracings alone, between *pulsus bigeminus* due to extrasystoles and *pulsus alternans* may be extremely difficult, not infrequently it is impossible In view of the entirely different clinical significance of these two phenomena the importance of a correct diagnosis needs no emphasizing In some instances the result of exercise is helpful· whereas after exercise extrasystoles tend to disappear temporarily, alternation usually becomes more pronounced

DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF PULSUS ALTERNANS

The essential clinical significance of *pulsus alternans* is that, as a rule, it indicates myocardial damage. When found with a slow heart rate this is invariably the case, whereas with higher rates, in particular 120 and more, it has sometimes been encountered in individuals without any other sign of cardiac disease, and it has also been observed during paroxysmal tachycardia in otherwise healthy subjects. According to Wenckebach and Winterberg alternation for a few beats after an extrasystole likewise occurs in healthy people. It may change from minute to minute and may appear and disappear without any known cause (Lewis, 1925)

In patients with hypertension alternans often is an early sign of heart failure

The prognostic significance depends on the underlying condition which gave rise to the *pulsus alternans* Thus, in myocarditis or toxic myocardial damage in diphtheria alternation may disappear concurrently with the recovery of the myocardium The same is also found after myocardial infarction In such cases the temporary occurrence of *pulsus alternans* cannot be said to have any lasting prognostic significance But even persisting alternating pulse, though in most cases a sign of serious prognosis, need not indicate the imminent breakdown of the circulation in every case Thus, one patient with *pulsus alternans* was observed for six years (Tabora) and another for five years (Swildens); the latter was under observation by one of us for two additional years when alternation was invariably present

UNDERLYING MECHANISM

Starting with Gaskell's work, a difference in the excitability of the individual myocardial fibres was widely regarded as the cause of alternation Originally, it was assumed that the large pulse is due to the contraction of all the ventricular fibres whereas the smaller one was thought to be produced by the contraction of only a fraction of such fibres This view was found not to explain all observations and Mines' explanation became more widely accepted. According to him, alternation is due to the alternating contraction of a greater and of a

smaller number of myocardial fibres, according to the formula $V\text{-}V_1$: $V\text{-}V_2$: $V\text{-}V_1$ . . . etc., whereby V stands for all the ventricular myocardial fibres, V_1 and V_2 for a smaller and a larger fraction, respectively, of fibres belonging to both ventricles. One of many variations of this view is that of Wenckebach (1901) and of Wenckebach and Winterberg, who laid the emphasis on small alternating differences in filling. Any theory to explain this phenomenon has to include the observation that alternation of contraction has been observed in isolated muscle strips (Weekers, Fredericq, 1913). For a discussion of the various theories the reader is referred to Kisch's monograph (1932).

SUMMARY

In accordance with Kisch, cardiac alternans is "defined as a regular alternation in the bio-energetic processes in the heart, occurring in two consecutive beats, and not being due to the regular alternation in the time sequence of the individual contractions" (our translation) It was included in this book for two reasons: first, from a historical point of view, because of the confusion between *pulsus alternans* and *pulsus bigeminus* due to extrasystoles, with its consequent effect on the ideas of the prognostic significance of these conditions; second, because extrasystoles greatly enhance alternation of the pulse The diagnosis and incidence of *pulsus alternans* are discussed and some relevant experimental investigations briefly reviewed. The relationship between extrasystoles and *pulsus alternans* is discussed in some detail and brief reference made to auricular alternans The cardiac phenomena of mechanical and electrical alternation are described The differentiation between *pulsus alternans* and *pulsus bigeminus* is discussed in some detail with special reference to difficulties encountered in cases of extrasystoles occurring late in diastole. The essential diagnostic and prognostic significance of *pulsus alternans* consists in its being an indication of myocardial damage, and in patients with hypertension it often is an early sign of heart failure. Instances are discussed in which temporary and even persisting alternating pulse may not be a sign of grave omen As far as the underlying mechanism is concerned Mines' explanation has become more widely accepted, according to which the phenomenon is due to the alternating contraction of a greater and of a smaller number of myocardial fibres belonging to both ventricles.

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CHAPTER VI

FLUTTER, FIBRILLATION AND PAROXYSMAL TACHYCARDIA

FLUTTER AND FIBRILLATION

General Remarks, applicable to Auricular and Ventricular Varieties

In this section we propose to demonstrate that the mechanism underlying flutter and fibrillation, both auricular and ventricular, is far more akin to that of ectopic beats and extrasystoles than commonly assumed until quite recently, in particular regarding the auricular variety A discussion of the *nature* of these arrhythmias is therefore pertinent in a book devoted to extrasystoles and allied arrhythmias. We do not propose, however, to include a description of the electrocardiographic appearances or clinical aspects of these conditions as they constitute separate and well-known entities which are fully discussed in the cardiological textbooks Only one familiar clinical observation may parenthetically be mentioned in order to illustrate the close clinical relationship between extrasystoles, and flutter and fibrillation, namely that auricular extrasystoles, particularly the multiform variety, often are precursors of auricular fibrillation, and the same holds good for multiple or multiform ventricular extrasystoles regarding ventricular fibrillation

Fibrillation was discovered much earlier than flutter, namely ventricular fibrillation by Hoffa and Ludwig in 1850 (pp 129 *seq*) and that of the auricles by Vulpian in 1874 Auricular fibrillation in man was established in 1909 by Lewis and by Rothberger and Winterberg Auricular flutter was first described experimentally by McWilliam in 1887 and in man by Jolly and Ritchie in 1911 It is thus understandable that the earlier theories dealt only with fibrillation The close relationship between fibrillation and flutter was emphasized by Rothberger and Winterberg in 1914

Of the various theories put forward to explain these disturbances of rhythm three may be mentioned as having attracted most attention

1 Theories based on the assumption of dissociated action of various groups of muscle fibres (Kronecker) The first indication of this view can already be found in the description of the discoverers of fibrillation (Hoffa and Ludwig, 1850), in which they say (regarding the entirely irregular rapid and weak movements of the heart on strong electrical stimulation): " The irregularity of these movements is due to the fact that the individual anatomical elements lose their relationship to one another and cease to contract simultaneously " (our translation)

Subsequently, the emphasis shifted to the nature of the impulses and their formation which produced such contractions

2 Theory of tachysystoly According to this, fibrillation is due to the rapid formation of stimuli in ectopic centres This hypothesis was based on Engelmann's view (1896) that in certain experimental conditions automatic stimuli arise in various groups of myocardial fibres which interfere with one another, affecting contractility and conduction, with the result that various kinds of arrhythmias are observed of which he mentioned fibrillation, " Wuhlen " and *delirium cordis* Hering (1900) considered ventricular fibrillation to represent the highest degree of enhanced ectopic impulse formation Winterberg (1907) attributed this condition to impulses originating in many centres, and the condition as a whole was aptly termed " functional fragmentation " by Lewis who also stressed the pathological

nature of the impulses which, at that time, he considered similar to, or identical with, those of extrasystoles (Lewis, 1913).

This " theory of polytopic stimulus formation " seemed supported by the observation that if a fibrillating ventricle was divided into several parts, fibrillation did not stop, but the fragments continued to fibrillate (Kronecker, Hering 1917, p. 22).

In further studies on the mechanism of fibrillation and flutter Rothberger and Winterberg (1914, 1916) pointed out that fibrillation may be found in the presence of a co-ordinated cardiac action and put forward the view that rapid stimulus formation in only *one* centre may suffice to produce fibrillation and flutter, they also stressed the close relationship between these two arrhythmias This view of a unifocal origin of ventricular fibrillation and flutter emphasized the fundamental similarity between the mode of origin of these two arrhythmias on the one hand and that of extrasystoles on the other.

Whereas none of the authors mentioned, nor others who held similar views (for example Kisch) specified the site of the presumed ectopic impulse formation, Haberlandt located it in the A-V region.

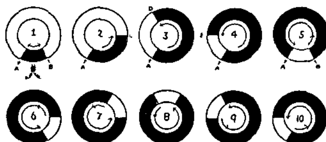


FIG. 142 [illegible]

[illegible]

Another objection against the theory of polytopic stimulus formation was based on the observation that fibrillation often stops suddenly, without any intermediate changes in the electrocardiogram If many centres were active, it was argued, their sudden simultaneous [illegible]

that fibrillation and flutter were due to a circus movement

3. Theory of circus movement. This is based on the fundamental experimental work of Mayer, Mines and Garrey who demonstrated that, in certain experimental conditions, one [illegible]

fibrillation is due to the brilliant work of Lewis and his collaborators.

The principle of the theory of circus movement is too well known to justify any further discussion. Fig 142 may serve to summarize the mechanism assumed to underlie this phenomenon (*see also* p 120).

Lewis and his collaborators attempted to prove in two ways that fibrillation and flutter are due to a circus movement. 1 Experimentally, by determining the order of activation of the auricles during flutter and fibrillation by means of direct leads. By this method they found that the main (" mother ") excitation wave circulated in the auricles through a path consisting of the *taenia terminalis* and around the large veins. Centrifugal " daughter " waves activated the auricular portions outside the range of the main wave It was, however, not possible to investigate the whole of this presumed path since the posterior part of the left auricle could not be fully explored 2. Clinically, by calculating the movements of the electrical axis of auricular activation in a case of auricular flutter by means of simultaneous records obtained with three special leads It was found that this axis rotated through a full circle of 360° around the great veins (Lewis, Drury and Iliescu)

From these investigations Lewis and his co-workers concluded that *auricular* flutter and fibrillation are due to a circus movement. In flutter a single circus movement was thought to exist which travelled " on a path repeated with much accuracy from cycle to cycle " (Lewis, 1925, p 340) In fibrillation a single circus movement again was assumed, " but the path followed is uneven, in its detail it constantly alters and sometimes, though for brief periods, the path changes more grossly, but in general the same broad path is used over and over again " (*Ibid*, p 341)

Regarding *ventricular* fibrillation, Lewis postulated a similar mechanism, but pointed out that there was no direct evidence of a wave circulating in the ventricles Garrey (1924), on the other hand, thought that in ventricular fibrillation circulating waves may occur at any place in the cardiac chambers, owing to areas of diminished conductivity which prevent the excitation wave from pursuing its normal path (*see also* below, p 230).

The further discussion can with advantage be divided into that of auricular, and of ventricular fibrillation and flutter

Auricular Flutter and Fibrillation

One of the reasons for the ready and widespread acceptance of Lewis's conception of auricular fibrillation and flutter was that the theory of circus movement afforded a plausible explanation of the conversion of flutter into fibrillation by vagal stimulation (Rothberger and Winterberg, 1914) It was known that vagal stimulation shortens the refractory period of the auricles, but Rothberger and Winterberg hesitated to assume that it also increases the rate of impulse formation The circus movement theory seemed to explain this effect, upon flutter, of vagal stimulation in a most satisfactory manner: The shortening of the refractory period abolished more quickly the " islands of refractoriness " of tissue—caused by the excitations following in quick succession—and thereby made it possible for the circulating wave to use shorter, because less circuitous paths, that is, stimulate the auricles at the faster rate of fibrillation as compared with the slower one of flutter This increase in rate of auricular stimulation as a result of shortening of the refractory phase can, however, be explained in a different way If it is assumed that the [illegible]

The stimulating effect, upon ectopic impulse formation, of acetylcholine (*q v*, p 328) is relevant in this context If a rhythmic stimulus is envisaged, shortening of the refractory phase may also cause a more rapid stimulus formation and stimuli would become suprathreshold at an earlier stage.

Objections against the circus movement theory were, however, raised at a very early

stage, particularly by Rothberger (1922), which, in view of recent developments, necessitate a more detailed discussion. The most important ones are:

1. As already indicated above, in determining experimentally the movements of the electrical axis in flutter Lewis could not examine the whole path since the posterior portions of the left auricle were inaccessible to such investigation. Rothberger pointed out that Lewis's assumption of the circulating wave's traversing that part of the circle was based *solely on calculation.*

2. The above argument of Rothberger gains in importance if it is realized that special investigations have failed to show the presence of muscle bundles in some portions of the left auricle (particularly near the orifices of the pulmonary veins) which would be necessary to complete the circular path assumed by Lewis to be traversed by the circulating wave (Rothberger, 1931)

3. The theory of circus movement assumed that it continues as long as there is a gap of excitable tissue between the head and tail of the circulating wave. It was therefore emphasized as an important point in favour of this theory that one strong electrical shock abolished auricular fibrillation, this being explained by the abolition of the gap by the shock. If this reasoning were correct every electrical stimulus strong enough to excite the whole auricle should always terminate immediately auricular fibrillation in this way, as a gap would have to be assumed to be continually present; this, however, is not the case. Mines wrote already in 1913 "This"—that is a single shock—"*if timed properly* instantly arrested both chambers . " (our italics)

4. According to Lewis, in the dog's heart during auricular fibrillation and flutter the main wave invariably travels up or down the sinus node. It would therefore have to be expected that interruption of this path by broad ligatures applied round the *taenia terminalis* should terminate auricular flutter In sixteen out of seventeen such experiments flutter persisted without any change in the shape of the F waves in the electrocardiogram. This observation is incompatible with a circus movement through paths postulated by Lewis (Scherf, 1928).

5 If flutter is experimentally produced by faradic stimulation the flutter waves usually have the same shape as the P waves of the sinus beats Moreover, if by certain experimental interferences changes in the shape of the P waves of the sinus beats were produced, subsequent flutter showed F waves of the same altered shape These observations suggest that flutter originated in the same area in which the preceding (or succeeding) slower rhythm arose (which was either sinus or A-V rhythm) and are incompatible with Lewis's assumption of a circus movement (Scherf, 1928)

6 The last observation (5) also tends to strengthen an objection which Rothberger had put forward against the validity of Lewis's conclusions from his clinical observations As stated above, by calculating the movements of the axis of auricular activation in a patient with auricular flutter Lewis, Drury and Iliescu found a rotation through a full circle Rothberger's objection to this was that the recorded waves, on which this calculation was based, were most *unlikely to have been due to the excitation of the tissue in the path of the circulating wave*, involving thin muscle bundles, but were due to the activation of the mass of auricular muscle. Rothberger contended, therefore, that it was not permissible to draw any conclusions about the course of a " mother " wave from deflections which are due to the whole of the auricular musculature The findings, listed above (5), emphasize the validity of Rothberger's argument, since in Scherf's experiments the changes in the P waves were effected by interferences applied at a considerable distance from the path of the " mother " wave as postulated by Lewis

7 It was found in the dog's auricle by Andrus, Carter and Wheeler that an electrical stimulus introduced during vagal stimulation shortly after the end of the refractory period could produce auricular fibrillation. This was observed also if the stimulus was applied

well out on the auricular appendix As there was no measurable gap between the stimulus and the beginning of the re-entrant rhythm these authors concluded that the excitation arose at the site of stimulation and " not in a ring of muscle at the base of the auricle " This observation is thus also not in accordance with Lewis's theory and is far better explained by repetitive impulse formation at the site of stimulation.

8. In some cases of disorders of auricular rhythm a sudden marked increase in the rate has been reported (flutter: Cookson and Clark-Kennedy, Parsonnet and Parent, A-V tachycardia Rosenbluth and Winterberg; auricular paroxysmal tachycardia: Camp and Scherf) Of these, we do not concur with the interpretation of the records given by Cookson and Clark-Kennedy, and Parsonnet and Parent Even if these were instances of a sudden doubling of the flutter rate, which we do not consider the published tracings demonstrate in any way convincingly, we could not accept the explanation that this is due to the excitation wave's suddenly pursuing a path of half its former length; this seems an entirely arbitrary assumption put forward to explain the records as interpreted by these authors In such cases the assumption of rapid stimulus formation with a former 2 : 1 response changing into a 1 : 1 response seems far preferable, as postulated in the case published by Camp and Scherf.

9 It has been observed that vagal stimulation during auricular fibrillation may suddenly increase the rate of stimulation to 2,000–3,000 per minute Lewis called this phenomenon rapid re-excitation and explained it by assuming that the circulating wave pursues a path with a very small diameter The path around the large veins is much too long to account for such high rates of re-excitation No explanation has been offered why and how a much shorter path is suddenly traversed by the excitation. Since it is known that faradic stimulation of the vagus may shorten the refractory phase of auricular tissue to one-fifth of its former value these very high rates of excitation can be explained by a fivefold increase in the rate of response of the auricle to a continuous stimulus, or a fivefold increase in the rate of rhythmical stimulus formation

These observations have been discussed in some detail in order to demonstrate that, [illegible]

doubts may be found in the reviews by Winterberg (1926) and by Rothberger (1931, p 707) De Boer's views are also shortly discussed by Rothberger (1923) and in the chapter on " Mechanism " (p 483)

In recent years series of experiments carried out by Scherf and his collaborators since 1946 with new techniques have yielded results which tend to prove that auricular fibrillation and flutter are due to the rapid stimulus formation in one centre, the former in certain conditions in several centres. Their observations are all incompatible with the circus movement theory which they can be considered to have disproved in the conditions of their experiments

In these investigations a method was employed to produce auricular arrhythmias which was described by Langendorff almost seventy years ago, namely the topical application of chemical compounds to the cardiac surface. Of these, aconitine was used in the great majority of these studies, namely application of a few crystals of pure aconitine to a small area at various points of the auricular surface, or by sub-epicardial injection of 0·05 cc. of a 0 05 per cent solution of aconitine *

By this method it was possible with great constancy to precipitate within one minute a regular auricular tachycardia with a rate of about 300 per minute. Cooling the site of

* This method of *topical* application of aconitine is distinct from the *systemic* use by intravenous injection of this substance, which was widely used in previous experiments of Scherf and co-workers a considerable time ago, see chapter on "Nervous System," p 255

application of the drug or separating it from the rest of the auricle by means of a clamp immediately abolished the tachycardia which re-appeared within 1–3 seconds after cooling was discontinued or the clamp removed. From these observations it was concluded that the ectopic auricular tachycardia originated in one focus, namely the site of application of aconitine Vagal stimulation during auricular tachycardia usually increased its rate, but auricular fibrillation was never observed in that series of experiments. Such arrhythmias presented some features suggestive of flutter, but "essential paroxysmal tachycardia" could not entirely be ruled out at that time (Scherf, 1947) It was, however, pointed out by the author already at the time that the results are not compatible with Lewis's circus movement theory if this tachycardia proved to be flutter. Similar arguments were put forward by Scherf in 1948 These studies were extended by Scherf, Romano and Terranova (1948) with the one important modification that aconitine was injected into the head of the sinus node In this series, as distinct from the former one, it was found that auricular fibrillation occurred spontaneously or was easily induced by vagal stimulation. Here again, cooling immediately abolished the arrhythmia which re-appeared when cooling was stopped The ready transition, in these experiments, of the auricular ectopic arrhythmia into auricular fibrillation, either spontaneously or as a result of vagal stimulation, as well as the observation that vagal stimulation never abolished it made it possible to determine the auricular arrhythmia as auricular flutter, as distinct from auricular paroxysmal tachycardia The result of these experiments could "only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center" (p. 250).

This view was supported by further experiments on the effect, upon such arrhythmias

subsided prior to these interferences (Scherf, Schaff and Gokien). It is known that stretching and pressure cause a more rapid depolarization, and increase the rate of impulse formation; but there is no reason to assume that they have any effect on conduction. This observation could hardly be understood if a circus movement is assumed, for it would be difficult to explain how pressure exerted with a thin probe on an area with a diameter of 2–3 mm. could produce an increase in rate of conduction of a circulating wave. An increased rate of impulse formation, on the other hand, is known to occur in nerves as a result of pressure and stretch, in the whole heart of frogs stretch was found to be associated with a negative potential (Rothschuh) which enhances spontaneous impulse formation (*see also* p 501) The inference from these experiments again was that such ectopic arrhythmias originate in a focus and are not due to a circus movement (Incidentally, these experiments may also have a bearing on the clinical observation that in certain clinical conditions exertion may precipitate auricular arrhythmias, *see* section on "Exercise", p 413)

Faradic stimulation of the cardiac sympathetic nerves was found to increase the rate of ectopic auricular tachycardias elicited by the topical application of aconitine to the sinus node or to various portions of the auricles. This effect was abolished by atropinization and attributed to increase in vagal tone by way of reflex (Scherf, 1949)

The view that such arrhythmias produced by aconitine originated in a circumscribed focus and were not due to a circus movement was strongly supported by further observations on the effect, upon the onset or recurrence of the aconitine tachycardia, of simultaneous cooling of the site of application of the drug, and faradic stimulation of the left vagus This abolished the flutter which, after cooling and vagal stimulation had been discontinued, gradually re-appeared. The constant shape of the P waves in re-appearing flutter of gradually increasing rate and the frequently observed longer intervals between successive P waves made it possible to exclude a circus movement with even greater certainty (Scherf

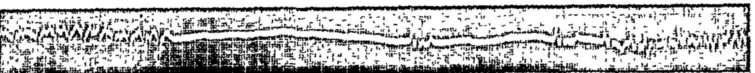


FIG 143 —From an experiment on a dog. The beginning of the record shows auricular fibrillation elicited by the sub-epicardial injection of aconitine into the head of the sinus node Abolition of the arrhythmia by cooling the site of application of the drug (middle of the record) with subsequent re-appearance of fibrillation when cooling was stopped (end of the tracing).

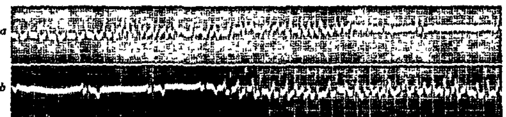


FIG 144 —From an experiment on a dog (25th March, 1947) *a*. Stretching of the wall of the auricle increased the rate of auricular flutter and converted it into fibrillation which was subsequently abolished by cooling the site of application of aconitine *b*. Re-appearance of flutter when cooling was discontinued

and Terranova, 1949). These experiments also showed that by cautious cooling auricular fibrillation could be converted into flutter and auricular extrasystoles.

Some of these observations are illustrated in Figs. 143–146.

The beginning of Fig 143 shows auricular fibrillation which had been precipitated in a dog by the sub-epicardial injection of aconitine into the area of the head of the sinus node. The remaining part of the figure shows the immediate cessation of fibrillation and restoration of sinus rhythm on cooling the site of aconitine application, and the subsequent re-appearance of fibrillation when cooling was discontinued.

Fig 144a shows in its beginning auricular flutter precipitated by aconitine. Stretching of the wall of the auricle immediately increased its rate to over 600 per minute and converted it into fibrillation This was promptly abolished by cooling the site of aconitine application After cooling was discontinued flutter re-appeared (Fig. 144b)

Fig. 145 was obtained from a dog in whom the topical application of aconitine had precipitated auricular flutter which subsequently disappeared (beginning of the tracing) Stretching of the auricle caused flutter to re-appear for the duration of the stretching

Fig. 146 shows auricular flutter with alternation in the duration of auricular diastole during vagal stimulation. Auricular flutter was produced by aconitine and before vagal stimulation the flutter rate was 270, every stimulus being conducted to the ventricles. During stimulation of the left vagus complete A-V block ensued and the reproduced alternation in cycle length was observed. The long intervals between every second auricular wave exclude the existence of a circus movement its long absence, amounting up to 0·45 second, and subsequent re-appearance would be inexplicable.

It could be argued that cooling of the site of aconitine application could abolish flutter also if this arrhythmia were due to a circus movement. But the immediate re-appearance of flutter, showing the same shape of the F waves as before its temporary suppression, constitutes strong evidence in favour of its origin in a circumscribed focus by way of rapid stimulus formation It would seem extremely improbable that a circus movement should immediately be resumed through identical paths after such temporary suppression; there are no grounds for the assumption that a circus movement could start again of its own accord in this way after it was interrupted And if, as in some experiments described above, such flutter waves were separated by longer intervals a circus movement becomes an impossibility.

With *focal* application of aconitine the presence of only one focus of stimulus formation is easily understood. It had to be expected that, whenever auricular fibrillation occurred after aconitine has been spilled over the auricle, or after its intravenous administration, more than one centre of stimulus formation would be active and that, in such circumstances, [illegible]

electrical stimulation of, or topical application of acetylcholine to, the auricles is not stopped [illegible]

[illegible] 1950a, Scherf, 1951). The results obtained in arrhythmias produced by electrical stimulation or topical application of drugs other than aconitine indicated that, in such conditions, more than one centre of rapid impulse formation is active, and that auricular fibrillation cannot be considered to be due to one uniform mechanism in all cases. Evidence will be discussed below in the section on ventricular fibrillation that rapid impulse formation in one ectopic centre may awaken that in others. But all these investigations point to rapid

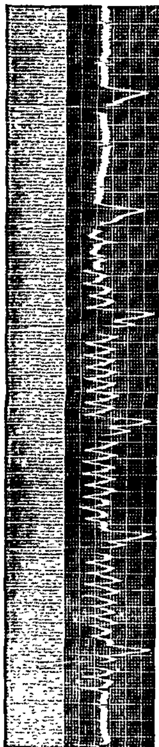


FIG 145 —From an experiment on a dog, Re-appearance of auricular flutter due to stretching the auricle, Complete A-V block is present owing to the severing of both bundle branches For further explanation, see text

impulse formation in one centre as the mechanism underlying auricular flutter, and to rapid impulse formation in one centre or in several centres as that underlying auricular fibrillation, while none are consistent with the assumption of a circus movement.

FIG 146.—From an experiment on a dog Auricular flutter with complete A-V block during vagal stimulation, with alternation in cycle length The two strips are continuous For further explanation, see text From SCHERF and TERRANOVA *Amer J Physiol*

Our view, a departure from the widely accepted theory of circus movement, has recently [illegible] They elicited auricular flutter [illegible] iat is by the method of Scherf [illegible] d to take any note of the work of Scherf and his collaborators, summarized above On the contrary· Their solitary reference to the paper by Scherf, Romano and Terranova is confined to the technical aspects only. Their (Prinzmetal *et al*) failure to mention the results and conclusions of Scherf *et al.* creates in those unfamiliar with that work the erroneous impression that they (Prinzmetal *et al.*) deserve the credit of priority *

While we consider disputes about priority undesirable we consider it equally undesirable that confirmatory work should, by omission of appropriate references, pose as original work. In this view we are confirmed by an Editorial in the *Ann. int Med* to which such readers are referred who wish to obtain an impartial representation of the issue

The claim of Prinzmetal *et al.* that auricular fibrillation caused by electrical stimulation can be suppressed by cooling the site of stimulation is at variance with the findings of Scherf *et al*, summarized above

Our own position can aptly be described by quoting Lewis " Relative to the writer, and in justice to the workers in my laboratory, I will here state emphatically that, *except where by reference it is specifically noted* there is no sentence in our long series of papers, nor for that matter in the present chapters, which would have been written differently had

his papers as a whole remained unpublished." (Lewis's italics, 1925, p. 295, footnote.) The only alterations necessary to make Lewis's statement fully applicable to the matter here under discussion consist in the substitution of the plural for the singular.

Ventricular Flutter and Fibrillation

Of the several varieties of flutter and fibrillation ventricular fibrillation was the one to be discovered first (*see* above). Ventricular flutter was discussed only relatively late and its separation from ventricular tachycardia is still far from clear.

It was realized at an early stage that fundamental differences exist between auricular and ventricular fibrillation. Some of the reasons are not far to seek. In the auricles the specialized system is concentrated in two nodes, whereas in the ventricles the specialized conducting fibres cover the whole endocardium and permeate the myocardium (*see also* section on " Spread ", p 370), the spread of the excitation through the auricles takes place radially through the common myocardium whereas, in the ventricles, it is effected by a separate system of paths, lastly, whereas auricular fibrillation is well compatible with life, the ventricular variety results in arrest of the circulation within the heart itself and changes the condition of the heart immediately

Ventricular fibrillation is probably the commonest cause of sudden death and the dramatic rôle thus played by this arrhythmia was found to stimulate numerous studies about its nature and prevention This important problem is, however, still far from solved.

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The theories of unifocal and multifocal (polytopic) ectopic impulse formation as the mechanism underlying auricular fibrillation were applied also to ventricular fibrillation, notwithstanding the recognized differences between auricular and ventricular musculature.

these two arrhythmias, pointed out that there was no direct evidence of a wave circulating in

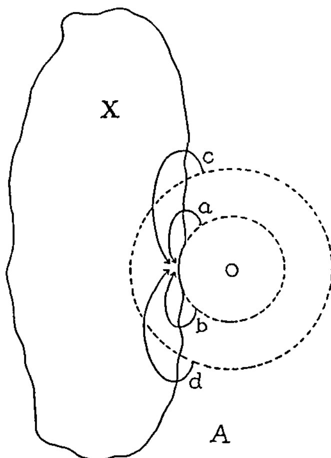


Fig. 147—From Ashman and Hull (1945). *Essentials of Electrocardiography* The Macmillan Company, New York For explanation, see text.

the ventricles. The suggestion "... put forward in unequivocal terms by both Mines and Garrey ..." (Lewis) that ventricular fibrillation is due to a circus movement was accepted by Lewis in view of the analogy of the phenomena observed in ventricular and auricular fibrillation. But far from considering this as the firmly established mechanism of ventricular fibrillation, Lewis wrote: "Much more work must be undertaken before we can hope to obtain really clear and detailed conceptions of the gravest disorders of the ventricle."

waves in ventricles of large dogs, and of inducing fibrillation in the cooled ventricle of the rabbit's heart by applying a stimulus just at the end of the refractory period. Independently Garrey developed a similar theory in the same year. Starting from the observations that in small animals (rat, rabbit) hearts usually recover from fibrillation whereas in large animals (dogs, calf) and in man the reverse is the case, and that a certain muscle mass is necessary to sustain fibrillation, Garrey assumed that fibrillation is due to circulating excitations in closed intramuscular paths, which can only be maintained in masses of adequate size and shape A unilateral spread of excitation is a prerequisite which Garrey assumed to be due to areas of local block.

This theory may be illustrated in the form in which it was accepted by Ashman and Hull (Fig 147). In this figure X indicates an area with a refractory period longer than that of the rest of the muscle O is the point of stimulation on the surface of the ventricle. With a weak shock applied at O the area indicated by the smaller circle is immediately excited, the excitation is assumed to penetrate slowly through the area of increased refractoriness (arrows a and b) and, when emerging from it, to encounter tissue which is still absolutely refractory so that it cannot re-enter the area of the (smaller) circle. The result is one extracontraction. If, on the other hand, a relatively strong stimulus is applied at O, a larger area, indicated by the larger circle, is immediately excited Again, the excitation wave is assumed to creep round, and slowly penetrate into, the zone X of increased refractoriness (arrows c and d), but by the time it reaches the boundary of the area which had previously been excited immediately (indicated by the periphery of the larger circle) this need no longer be refractory so that the excitation wave re-enters this circle and thus spreading out from X re-activates the whole ventricle As the whole contraction was premature, the refractory period of X, as elsewhere, is shorter than normal which facilitates re-entry of the impulse through the paths indicated by arrows c and d

Our objections against the circus movement theory of ventricular fibrillation can be summarized by stating that, not only is such assumption purely hypothetical without any experimental proof, but also observations made during the last ten to twelve years have emphasized the importance of the vulnerable period and of repetitive response to single or continuous stimuli in accounting for the initiation of ventricular fibrillation. The theory

phenomena more fully in the chapter on " Mechanism " In the present context it is pertinent to recall the investigations of Wiggers and Wégria who demonstrated that only stimuli falling up to about 0 06 second before the end of contraction (marked by the incisura in the intra-ventricular pressure curve) produced ventricular fibrillation. Stimuli applied during the isometric relaxation period or subsequent phase of diastole never yielded ventricular fibrillation, but only premature beats The vulnerable period extended through a considerable portion of late systole, corresponding roughly to the T wave of a standard electrocardiogram By means of studying local electrograms obtained with three pairs of contiguous electrodes, it was subsequently found by the same school of workers (Moe, Harris and Wiggers) that fibrillation elicited by a very strong brief D C. shock was preceded by discrete deflections recurring at progressively decreasing intervals By investigating the order of excitation on the surface and interior of the ventricles during such beats it could be shown that these discrete ectopic beats were due to repetitive emission of several impulses from the stimulated area and were not due to a re-entry mechanism. Similar conditions were found to prevail regarding the beats initiating ventricular fibrillation produced by anodal polarization (Harris and Moe) In contradistinction to anodal polarization, the cathodal one was found ineffective in initiating ventricular fibrillation and this was attributed to the reduction in accommodation by anodal polarization (which is increased by

cathodal polarization). (Regarding accommodation, *see* chapter on "Mechanism", p. 504.) The reduction in accommodation was also found to be important to account for the observation that local cooling facilitates the development of ventricular fibrillation as a result of single threshold shock stimulation of a non-cooled region during early diastole (Hoff and Stansfield) The ventricular fibrillation itself, however, as distinct from the initiating series of ectopic beats, is assumed by Harris, Wiggers and co-workers to be due to a re-entry of impulses, attributable to a progressive decrease in the refractory period combined with a progressive increase in conduction time (Moe, Harris and Wiggers) Regarding ventricular fibrillation produced in dogs by coronary occlusion, Harris and Rojas demonstrated that a mechanism very similar to that in ventricular fibrillation caused by galvanic current prevails and that the partially ischaemic border seems to be the zone of origin of the ectopic beats. Multiple factors are, however, responsible for ectopic arrhythmias, including ventricular fibrillation, occurring after coronary occlusion, of which sympathetic nerve excitation is one (Harris, Estandia and Tillotson).

This problem was investigated in dogs by Scherf *et al.* (1950b) by means of the topical application of aconitine crystals to an area of the ventricular surface. This resulted within a few minutes in the appearance of ventricular ectopic beats which soon changed into a ventricular tachycardia of three hundred or more, resembling ventricular flutter. Whenever [illegible] then [illegible] 148. [illegible] into ventricular fibrillation and sometimes, but not always, this transition was preceded by a sudden increase in rate of the tachycardia. Once ventricular fibrillation was established cooling of the site of aconitine application, or of any other portion of the ventricular surface, had no effect on the arrhythmia From this the authors inferred that other centres of rapid ectopic impulse formation had become active so that cooling of one centre could no longer abolish fibrillation. That during ventricular tachycardia other centres may become active is certain; Fig 149 provides an illustration Both Figs. 149a and 149b show at their beginning ventricular tachycardia, elicited by the application of aconitine to the right ventricle. Cooling immediately abolished this tachycardia which is replaced by a slightly slower ectopic tachycardia originating in the contralateral ventricle Similar observations had been made by Scherf (1926) in a different context though interpreted differently at the time.

This seems to us to suggest that the primary disturbance in ventricular fibrillation is the rapid impulse formation in several ectopic centres, and that the local re-entries and interferences between such contractions are due to the rapid impulse formation in several centres, but not to a circus movement. While Wiggers and his co-workers put the emphasis on the progressive increase in conduction time associated with a reduction in the refractory period, resulting in local block areas and circus movements, we would stress the simultaneous activity at a high rate of several ectopic centres as the essential prerequisite.

Without wishing to enter into a detailed discussion of all points which have been adduced in support of the circus movement theory of ventricular fibrillation, two may be singled out as having been considered by some to be particularly important.

1. The observation that a certain muscle mass is necessary for fibrillation to occur was [illegible] Scharf and Goklen; Scherf *et al.*, 1950b). It is only with rates above a certain figure that precisely as a result of this high rate of impulse formation the islands of refractory tissue occur which Lewis, Feil and Stroud have demonstrated in such conditions (*see also* Lewis's



FIG 148.—From an experiment on a dog Ventricular tachycardia precipitated by the topical application of aconitine crystals to an area of the ventricular surface Suppression of the tachycardia by cooling the site of application with subsequent re-appearance of the tachycardia after cooling was discontinued

a

b

FIG 149.—From an experiment on a dog. The beginning of both strips show ventricular tachycardia elicited by the application of aconitine to the right ventricle. Its suppression by cooling the site of application resulted in a ventricular tachycardia originating in the contralateral ventricle

diagrammatic illustration 1921; 1925, Fig 306). In our opinion it is the high rate of impulse formation which is the primary factor. A certain muscle mass is necessary for a sufficient number of islands of refractory tissue of the requisite size to occur. We do not dispute the possibility, or even probability, of local re-entries in established fibrillation, but we do not believe that local circus movements either initiate fibrillation or are the primary factor in perpetuating it.

2. The termination of ventricular fibrillation by a strong electrical shock has been held to prove a circus movement underlying this arrhythmia, it being assumed that the termination is due to abolition of the " gap " of excitable tissue between the head and tail of the circulating wave. We have already drawn attention to one objection to this interpretation in connexion with auricular fibrillation, namely that only a shock *properly timed* has this effect. If the above reasoning were correct such shock should always terminate fibrillation, irrespective of its timing, which is not the case. It may here be added that, if a focal origin of impulse formation is assumed to underlie ventricular fibrillation, the abolition by a properly timed shock can be understood in a variety of ways For instance, depolarization of the foci with consequent change in the sequence and rate of impulse formation, so that excitations *no longer occur at the same rate or fall within the supernormal phase of preceding beats* would be one possibility.

In conclusion we may state our belief that none of the observations made in connexion with the initiation and establishment of ventricular fibrillation can be regarded as proving an underlying circus movement, many objections against this theory are discussed in this section On the other hand, we are not aware of any observations which could not be understood as the result of rapid impulse formation in circumscribed foci, resulting in local areas of depressed conductivity and local re-entries, these being due to the high rate. Such conception is in accordance with a wealth of observations made on nerve and cardiac muscle; of the latter, the work of Lewis and collaborators, published over thirty years ago, is not the least important.

Repetitive response to single and continuous stimuli is more fully discussed in the chapter on " Mechanism "

SUMMARY

The three main theories of the mechanism underlying auricular and ventricular flutter and fibrillation are briefly reviewed, namely, the theory of dissociated action of *various* groups of muscle fibres, that of tachysystoly, and of circus movement. The reasons are discussed why until recently the circus movement theory was widely accepted to explain *auricular* flutter and fibrillation, in spite of weighty objections raised against it almost from the start; these are discussed in some detail. More recent work, employing the experimental production of such arrhythmias by means of the topical application of aconitine, have yielded results which are incompatible with the circus movement theory and strongly suggest that auricular flutter is due to the rapid impulse formation in one circumscribed ectopic centre. This work is discussed in detail Auricular fibrillation cannot be [illegible]

[illegible]

mation occurs in several ecto [illegible]
of the " vulnerable period " [illegible]
alone single stimuli produce [illegible]
instance of repetitive response to a single stimulus; some relevant work on this is discussed, whilst the reader is referred to the chapter on " Mechanism " for a fuller discussion of this

phenomenon The observation is described and illustrated that, during ventricular tachycardia, the activity of one ectopic centre may awaken that of others. Evidence is discussed in support of the view that, in ventricular fibrillation, the primary factor is the simultaneous activity at a high rate of several ectopic centres of impulse formation, resulting in local areas of depressed conductivity and local re-entries, but is not a circus movement.

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PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is universally regarded as an arrhythmia due to a number of extrasystoles occurring in succession. The close relation between this disturbance of rhythm and extrasystoles has been recognized for a long time and is discussed in several papers published at the beginning of this century (Mackenzie 1902, Hoffmann 1903, Pan 1904, Lewis

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as well as ventricular ones are well known, the last usually having a far more serious prognostic significance than the others.

Many varieties of paroxysmal tachycardia have been reported. Thus this arrhythmia may occur in association with complete A-V block (Singer and Winterberg, Barker *et al.*, Case 16) or with ventricular extrasystoles (Samet and Schott); ventricular paroxysmal tachycardias with retrograde conduction to the auricles have been reported, often with some degree of retrograde block (Allan; Mahaim and Barrelet). The duration of the attacks may vary from a few seconds to many hours or even days, and equally great variations occur in their rate of incidence. It is therefore no exaggeration to say that there are no two patients in whom such attacks are identical, but in the same patient the same kind of attack may be observed over many years.

Since the essential reason for including paroxysmal tachycardia in this book is the close association of this arrhythmia with extrasystoles, a detailed discussion of the countless varieties of its features would be outside the scope of this book. A few special types may, however, be briefly discussed

It was Gallavardin to whom credit is due for having described many important forms of this arrhythmia. According to him (Gallavardin, 1922a) the classical variety (type Bou-

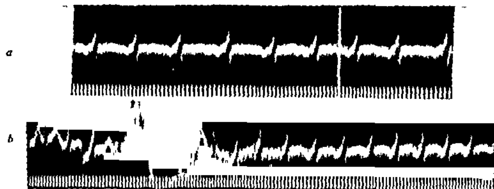


FIG 150 — Paroxysmal tachycardia arising in the coronary sinus area *a*· before exercise, rate 136. *b*. after twenty genuflexions, increase in rate to 214

veret) has no relation to single extrasystoles since no isolated ectopic beats are observed between attacks in such patients While this is true for quite a proportion of instances we do not think that, from a point of view of underlying mechanism or clinical significance, any distinction is justified between those cases and others in whom occasional isolated extrasystoles are recorded

Gallavardin described two further types of paroxysmal tachycardia which, in our opinion, constitute definite clinical entities:

1 The "*tachycardie à centre excitable*" (Gallavardin, 1922a) In this variety the individual attack is short and can easily be elicited by exertion or emotion Exertion may lengthen the duration of such attacks as well as increase their rate. Ventricular (Scherf and Weissberg, Wenckebach and Winterberg, Wilson *et al*) and auricular (Scherf and Weissberg) varieties of this arrhythmia have been described

Fig 150 shows such an instance in which the arrhythmia originated in the coronary sinus Exertion (20 genuflexions) increased the rate from 136 to 214 per minute

2 "*Extrasystolie à paroxysmes tachycardiques*" was described in its auricular and ventricular varieties by Gallavardin in the same year (1922b, 1922c). This type is characterized by the features that the individual paroxysm is short, consisting of series of 20–200

extrasystoles in succession, such paroxysms being separated by only a very few sinus beats, often only one, rarely more than three. Clinically, the individual attack is therefore short, lasting not more than a minute or two, but as soon as one attack stops the next one starts after a very brief respite. One peculiarity of this condition is that it tends to continue in the same fashion for many years Gallavardin observed a patient with the ventricular variety for seven years, we followed one with the same condition for five years Another patient with auricular paroxysmal tachycardia of this kind was under our observation for six years, and Parkinson and Papp—who called it repetitive paroxysmal tachycardia—reported such paroxysms during ten years of an eighteen years' period of observation.

Fig. 151 provides an example of the ventricular form of this arrhythmia and clearly *demonstrates the shortness of the attacks, separated by only one sinus beat.*

Fig. 152a illustrates the auricular variety, emphasizing also the diagnostic difficulties. Actually, in the report of the cardiographic department of the hospital where a first short record was obtained from this patient, a diagnosis of S-A block was made Longer records, reproduced in Fig 152a, show, however, that what might appear at first sight to be S-A block, is in fact normal sinus rhythm The P waves of the tachycardia resemble the sinus

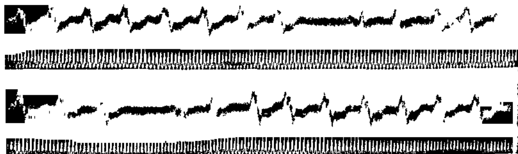


FIG 151 —Extrasystolie à paroxysmes tachycardiques ventricular form The two strips are continuous

P waves so closely in most leads that sinus tachycardia seems to prevail. While close inspection of the P waves during tachycardia reveals in some leads only some minute differences in shape, compared with the P waves during slow cardiac action, these are fairly obvious in lead CR-1 in which the P waves of sinus beats are high and peaked whereas those during tachycardia are much lower and round. Comparison of Fig. 152a with 152b, recorded from *the same patient one week later during sinus rhythm, confirms the diagnosis* that the condition reproduced in Fig 152a was, in fact, auricular " extrasystolie à paroxysmes tachycardiques ".

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attacks disappear after a varying period of time, in others the tachycardia gradually produces cardiac dilatation, with relative mitral and tricuspid regurgitation, and may terminate in death due to congestive heart failure (Scherf and Kisch) We would therefore advocate a somewhat more guarded prognosis. This is also justified in view of the notorious difficulties in the treatment of this arrhythmia which responds poorly or not at all to quinidine or digitalis. And even in those cases which do react favourably to one or the other of these

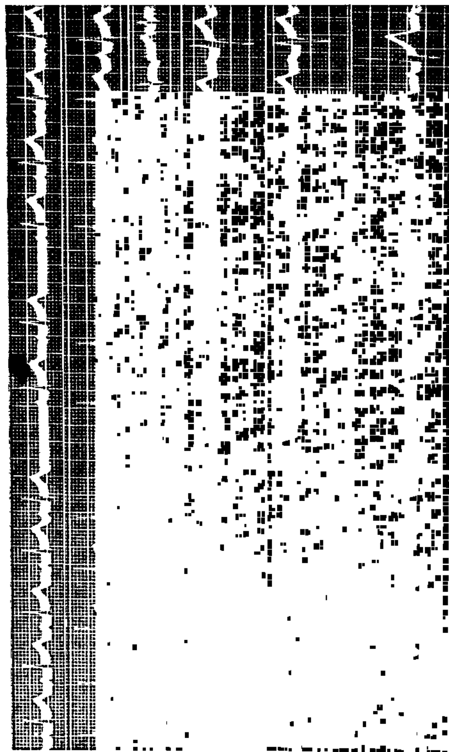


FIG 152*a*
Extrasystole à paroxysmes tachycardiques, auricular form

drugs, neither can be given indefinitely and as soon as the effective remedy is stopped the arrhythmia recurs

Tracings of this type of tachycardia are also reproduced in Figs. 175 and 200

Practically the same variety of paroxysmal tachycardia has also been termed " tachycardie en salves " (Gallavardin and Dumas 1924, Gallavardin and Veil 1927, 1929 a and b, Lutembacher 1929).

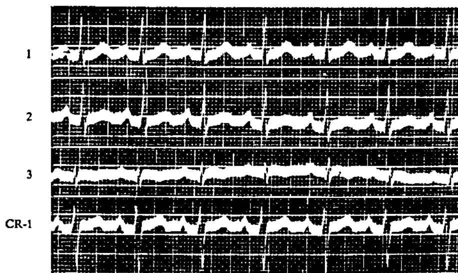


Fig 152*b*

From the same patient as Fig 152*a*, recorded one week later, sinus rhythm For further explanation, see text

Paroxysmal Supra-Ventricular Tachycardia with A-V Block

Until recently, it was thought that, with rare exceptions, in supraventricular paroxysmal tachycardia the ventricles respond to every supraventricular stimulus This was, in fact, considered to be one of the essential differences between paroxysmal tachycardia and auricular flutter, as in the latter some degree of A-V block, constant or varying, is nearly always present. While sporadic cases of paroxysmal tachycardia with A-V block had been reported since Koplik's first communication in 1917, it was realized only in 1943 that this condition *is by no means rare*, when Barker, Wilson, Johnston and Wishart collected seventeen such cases from the literature and added eighteen observations of their own In a subsequent paper they reported alternation of cycle length in this type of arrhythmia, which they interpreted as suggesting a circus movement with involvement of either the S-A or the A-V node (Barker, Johnston and Wilson; Barker, Wilson and Johnston). This group of workers amplified this conception by stating that such circus movement is of a special kind for the following reasons: slowing of the auricular rate and termination of the attacks by vagal stimulation and by digitalis, acceleration of the rate by exercise, the relatively slow rate and long cycle length, and the separation of the auricular deflections by isoelectric intervals (Regarding our views on this, *see* below) In the same year Decherd, Herrmann and ... Decherd and ... iated with ... ock: such ... with A-V

block (28·6 per cent) compared with only two in seventy cases without block. In view of the theory, then generally accepted, that auricular flutter and fibrillation were due to a circus movement, such observations tended to suggest that paroxysmal tachycardia, at least the variety with A-V block, was due to the same disturbance. Evans, who reported a series of twenty-seven cases of paroxysmal tachycardia with A-V block, emphasized the unity between paroxysmal tachycardia and auricular flutter. However, by determining the momentary atrial electrical axis for each 0·01 second Decherd, Ruskin and Herrmann failed to find any evidence of circus movement in this arrhythmia and concluded that "the weight of evidence points to the existence of an ectopic site of impulse generation". These authors also found considerable differences in the momentary atrial electrical axis between paroxysmal tachycardia with A-V block and auricular flutter (See also Fig 163*a*.)

Fig. 153 illustrates a comparatively rare variety of this arrhythmia, namely paroxysmal supra-ventricular tachycardia with periodically dropped ventricular beats (Wenckebach's periods). It was recorded in a man with rheumatic mitral and aortic valvular disease.

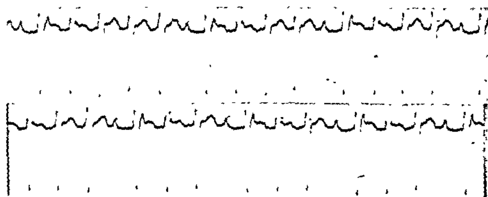


Fig 153—Lead V-1 The two strips are continuous. Paroxysmal supra-ventricular tachycardia with periodically dropped ventricular beats (Wenckebach's periods)

It should be recalled that the above conclusions in respect of paroxysmal tachycardia with A-V block were drawn at a time when the theory of circus movement of auricular flutter was almost universally accepted If, in spite of the closer association between paroxysmal tachycardia with block and auricular flutter no evidence of circus movement was found in the former, such mechanism would *a fortiori* seem far more unlikely to account for the ordinary variety of paroxysmal tachycardia without block. However, this problem is still controversial and its general aspects warrant a more detailed discussion

Mechanism of Paroxysmal Tachycardia

At the beginning of this section the close association between extrasystoles and paroxysmal tachycardia is emphasized; the borderline between multiple extrasystoles and a short attack of paroxysmal tachycardia is but vaguely defined Any attempt to explain the mechanism of paroxysmal tachycardia must have as its starting point the conception that this disorder of rhythm consists of a series of extrasystoles occurring in succession. "Thus we seem justified in regarding paroxysmal tachycardia and extrasystoles, at all events in their usual forms, as alike genetically." Lewis, 1925, p. 386. Lewis also pointed out that this idea was originally mooted by Hoffmann (1903).

In regard to the mechanism underlying these arrhythmias Lewis, the protagonist of the theory of circus movement in auricular flutter and fibrillation, later saw difficulties in applying this explanation to paroxysmal tachycardia, the crucial obstacle being that the "auricle has no sufficient tract of tissue to maintain a simple circus movement for a half second, if a reasonable conducting rate is allowed" (1925, p. 397).

In contradistinction to the very cautious way in which Lewis discussed the mechanism of this arrhythmia, Ashman and Hull, while not denying that occasionally it may be due to a rapidly acting ectopic pacemaker, considered a circus mechanism often, though not always, responsible. They thought it probable that in the auricular variety the circuit is into and out of the S-A node, whereas in the junctional type it was probably often due to an impulse re-entering the A-V node. In support of this view they pointed out that the termination of such attacks by vagal stimulation could easily be understood by the strong vagal effect on these nodes whereas such vagal action was inexplicable if ectopic focal impulse formation were assumed. While, for reasons discussed below in this section, we do not think that a circus movement underlies paroxysmal tachycardia, we admit that the effect of vagal stimulation in terminating such paroxysms is difficult to understand, a tentative explanation is mentioned below As already stated, Barker *et al.* also favour the conception of a circus movement being responsible for paroxysmal tachycardia in view of their observation of alternation of cycle lengths during the paroxysms since there were "no published examples of alternation in cycle length which have been clearly shown to depend solely upon the discharge of impulses by a single centre". However, since this statement was made it has been demonstrated that ectopic stimulus formation in a centre may be associated with alternation in cycle length (Scherf and Terranova, *see* Fig 146; Scherf, Chick *et al*)

While we believe that in some rare cases a circulating excitation may produce tachycardia in the manner discussed in connexion with return extrasystoles (*q v.*), the vast majority of instances of paroxysmal tachycardia are in our opinion due to ectopic impulse formation. *This view is based on the following considerations*

1 To a certain extent the circus movement theory as an explanation of paroxysmal tachycardia has been considered in view of the analogies between this disorder of rhythm and extrasystoles, flutter and fibrillation Since, for reasons fully discussed in the appropriate sections and chapters, we do not believe that, with rare specified exceptions, any of these arrhythmias are due to a circus movement, but are a result of ectopic impulse formation in a circumscribed centre, this argument becomes invalid

2 Warming of the focus of origin of extrasystoles elicited by the topical application of various compounds (sodium or barium chloride, digitalis, or strophanthin) results in paroxysmal tachycardia which lasts for the duration of the warming of the focus. This and similar observations, discussed in the chapter on "Mechanism", strongly support the focal origin of such arrhythmias and cannot be reconciled with the theory of circus movement.

3. The order of the cycle lengths between individual beats during paroxysmal tachycardia, particularly in the auricular variety, precludes a circus movement. This point, based on Lewis's views discussed above, seems to us a very strong argument against the circus *movement theory*

4. The observation of a sudden doubling of rate during paroxysmal tachycardia from 107 to 214 (Camp and Scherf) (*see* Fig. 154) contains two arguments against the circus movement theory: a rate of 107 cannot be due to a circus movement in view of the long cycle length (0·56 second), moreover, a sudden change of path of the presumed circus movement to one of half the former length is an assumption which is unacceptable for the same reasons which were discussed in presumed similar conditions of auricular flutter (p. 223). This observation is far better explained by assuming ectopic focal impulse

FIG 154.—Sudden doubling of rate during paroxysmal tachycardia From CAMP and SCHERF *Wien Arch inn Med*

formation, whereby during the slower rate either a 2 : 1 block was present or every second impulse failed to be initiated (*see* chapter on " Mechanism ").

5 The sudden dropping of a beat during tachycardia is incompatible with the circus movement theory Such observations were made in cases of auricular (Gallavardin 1946, Figs. 70 and 71 on pp. 130/1) and ventricular (Fig. 108) tachycardia. This phenomenon can be understood by assuming rapid focal ectopic impulse formation with occasional block, or occasional failure of one impulse to be initiated.

6 The observation that paroxysmal tachycardia may be associated with dissociation with interference (Schott) (Fig 155) can hardly be understood in conjunction with a circus movement, but presents no difficulty if focal impulse formation is postulated

We therefore believe that the series of ectopic beats, which constitute paroxysmal tachycardia, originate in the same way as we assume all extrasystoles (in the strict sense of the term) to arise, namely by being precipitated in an ectopic focus by the last preceding beat With the exception of the first beat of such paroxysms, which is an extrasystole with fixed coupling initiated by a sinus beat, the only difference is that in paroxysmal tachycardia the precipitating beat also is of ectopic origin In our opinion all these beats arise in the

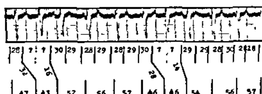


Fig 155—Lead CR-1 Paroxysmal auricular tachycardia with dissociation with interference From Schott *Proc roy Soc Med*

same circumscribed ectopic focus A circus movement not only is not proved, but—apart from rare exceptions—is unlikely in view of *all* the evidence which we are discussing against this theory in connexion with extrasystoles

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arrhythmia and restores sinus rhythm, or has no effect In clinical flutter, on the other hand, carotid sinus pressure never has this effect, and in experimental flutter vagal stimula-

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and Mueller) faradic stimulation of the vagus abolished flutter in rare instances. While we believe that the different clinical response of these two arrhythmias to carotid sinus pressure alone justifies a separation between these two groups of auricular arrhythmias—the unity of which tends to be emphasized of late—a satisfactory explanation of the mechanism accounting for the difference in vagal action cannot be offered. The tentative hypothesis

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Differential Diagnosis

While the general diagnostic principles of paroxysmal tachycardia will not be discussed a few remarks about differential diagnosis should not be amiss

The differential diagnosis of an individual attack of tachycardia of this kind must be made

(a) between paroxysmal tachycardia and other disorders of rhythm associated with a high ventricular rate, and

(b) between the various types of paroxysmal tachycardia according to the site of origin of the ectopic beats

Regarding (a) In practice, the most frequent difficulty arises in the differentiation between paroxysmal tachycardia and auricular flutter, which, at the same time, presents also the greatest theoretical difficulties In both, the ventricular rhythm may be regular or irregular and in both often is regular Until it was realized that A-V block is not infrequently associated with paroxysmal tachycardia these two arrhythmias were separated by the presence or absence of A-V block, this distinction is now no longer valid While we believe that these two arrhythmias are separate entities, because an attack of paroxysmal tachycardia can often be stopped by way of reflex whereas all such procedures are without effect in flutter, we prefer to admit that none of the criteria adduced for making the distinction electrocardiographically can be considered reliable (*see*, for instance, Israel and Mazzei) To cite just one example According to Evans in auricular flutter the auricular rate is slower than in paroxysmal tachycardia whereas according to Decherd *et al* (1943) the reverse is the case We consider it necessary to await the result of further studies before considering it possible to state distinguishing criteria with any degree of certainty Fortunately, this gap in our theoretical knowledge does not interfere with treatment

Regarding (b) The site of origin of paroxysmal tachycardia can often be determined by the usual electrocardiograms, particularly by chest leads taken from points 1 (and 2) or special chest leads (manubrium-xiphoid) In auricular paroxysmal tachycardia the ventricular complexes often are of normal shape, but aberrant intraventricular conduction of supraventricular impulses may closely simulate ventricular origin of the tachycardia Furthermore, in a considerable proportion of cases the P waves are buried in the QRS complex or T wave of the preceding beat and thus not discernible; this may lead to the erroneous diagnosis of atrio-ventricular tachycardia Unless auricular origin can definitely be excluded by special leads, of which oesophageal leads must be mentioned as being particularly valuable in all kinds of auricular disorders of rhythm, it is preferable to use the term supraventricular tachycardia The same considerations obtain as in auricular extrasystoles (*see also* section on " Incidence ")

Regarding the differentiation between supraventricular tachycardia with aberrant intraventricular conduction and ventricular tachycardia, the finding of a slower independent auricular rhythm, associated with a fast ventricular one with abnormally shaped complexes, establishes the diagnosis of ventricular origin This is, however, not possible in every case Another distinguishing factor can be established if isolated extrasystoles are observed between attacks these are usually from the same focus which gives rise to the tachycardia

That retrograde conduction may occur in ventricular tachycardia has already been referred to earlier in this section

From the point of view of prognosis and treatment the essential pre-requisite is to determine whether an attack is supra-ventricular or ventricular in origin

Treatment

Supra-Ventricular Paroxysmal Tachycardia

In the common variety of such attacks, that is without A-V block, the first approach should always be to stop the tachycardia by one of the manoeuvres which often terminate such paroxysms by way of reflex, the efferent path being the vagus It is true that, as discussed in the chapter on extrasystoles and the nervous system, stimulation of vagus or sympathetic may abolish or precipitate ectopic arrhythmias also in man, but in clinical practice stimulation of the vagus by way of reflex as a rule terminates ectopic supra-ventricular tachycardias whereas that of the sympathetic, for example by adrenaline, usually has the reverse effect

The most important methods for eliciting such Reflexes in clinical practice are.

1 CAROTID SINUS REFLEX Pressure is applied *exactly* at the site of the bifurcation of the carotid artery The correct level is found by determining the point of intersection of the carotid artery with the horizontal at the level of the upper border of the thyroid cartilage, but as the exact site of the carotid sinus varies somewhat in different individuals attempts at compressing at a slightly higher or lower level have to be made if the first trials are unsuccessful It is best to put the four fingers of one's hand behind the patient's neck and exert pressure with the thumb by gently but firmly compressing the artery downward and medially towards the spine. In the majority of cases pressure on the right is more successful than on the left, but in a minority the reverse is observed Pressure should always be carried out with the patient in the supine position and never on both sides simultaneously While pressure is exerted the heart action should be kept under observation by auscultation and pressure immediately released when the tachycardia stops, if this occurs it does so suddenly

The degree of pressure which has to be employed varies greatly in different patients. In elderly subjects with arteriosclerotic arteries merely touching the skin over the carotid sinus may terminate an attack; in others stronger pressure maintained up to half a minute may be necessary Untoward effects arising from carotid sinus pressure have been reported, for instance fainting, hemiplegia or dangerous cerebral anoxia, but these can be minimized by strictly adhering to the rules mentioned above Special caution is necessary in patients with pronounced arteriosclerosis

The proportion of attacks which can be terminated in this way is considerable If this method is at first unsuccessful it may prove effective if repeated after a time, particularly if in the meantime the patient was given quinidine or digitalis (*see* below) But drug treatment should be resorted to only after carotid sinus pressure and similar procedures discussed immediately below had been given a fair trial, in our opinion drugs are often given unnecessarily.

Most observers agree that carotid sinus pressure is ineffective in cases of ventricular paroxysmal tachycardia and this is easily understood in view of the absence of a direct vagal effect in the mammalian ventricle Exceptions to this rule have, however, been reported Thus, in an observation published by Wenckebach and Winterberg (1927, Plate 190) carotid sinus pressure precipitated as well as suppressed ventricular tachycardia Other unusual [illegible] the transient development of ventricular tachycardia before restoration [illegible]

2. OCULO-CARDIAC REFLEX. This manoeuvre may abolish an attack in patients in whom other procedures had failed to do so. The patient is asked to look downward and close his eyes; pressure is then exerted simultaneously on both eyeballs.

3 PULMONO-CARDIAC REFLEXES The simplest of these is precipitated by taking a deep breath Not infrequently this suffices to stop an attack In one of our patients, a seventy-two-year-old lady who for many years had an average of sixteen attacks a day, every paroxysm could be terminated in this way In his textbook on cardiac diseases Bamberger mentioned this measure as early as 1857. In some comparatively rare cases deep breathing precipitates such attacks. In other patients Valsalva's experiment is successful while deep breathing has no effect; this manoeuvre, too, may in rare instances fire off such attacks (Galli)

4. OTHER REFLEXES One of the most useful measures is the gagging reflex, elicited by the patient's putting his fingers in his throat It is as effective as vomiting which some authors advocate to induce artificially by drugs (for example, apomorphine), but without the undesirable side effects

In some patients attacks of supraventricular tachycardia can be stopped by deep bending, crouching, pressure on the abdomen or drinking iced water

Different individuals vary greatly in their response to any of these measures and each patient soon finds out for himself which is the most effective They all have this important point in common that the patients can learn to carry out themselves whatever manoeuvre they have found best The psychological effect of this, in addition to avoiding by the timely termination any somatic effect caused by prolonged attacks, is by no means negligible.

Drugs Drugs should only be employed if all the above measures have been tried, not only at the beginning of an attack, but at intervals during such paroxysms, and failed Moreover, such procedures may become successful when resumed in conjunction with drugs

There is hardly a drug which has not been mentioned as successful in suppressing such attacks, but in practice only three can be recommended. quinidine, digitalis and magnesium sulphate, in this order

Quinidine. As initial dose we recommend quinidine sulphate 0 2-0 4 gramme by mouth, to be repeated at intervals of three hours as long as necessary and provided no signs of cinchonism occur (*see* section on " Treatment ", p 475) In the majority of patients this regime will terminate the attack within a short time If necessary the above dose can be repeated one hour after the initial dose, or given at two-hourly intervals

In patients with frequent attacks preventive treatment by giving 0 2 gramme every four hours is often successful If necessary medication is continued during the night. It is not at all rare to find that after a time medication can gradually be reduced and subsequently discontinued without attacks recurring

The intravenous injection of quinine or quinidine is not free from risk and hardly ever necessary. Only in patients with greatly prolonged attacks in which the arrhythmia aggravated pre-existing heart failure to the point of danger should this method be considered which can yield spectacular results (Samet and Schott). The single dose varies between 0·2 and 0 5 gramme

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paroxysmal tachycardia develops after coronary occlusion and, contrary to the popular belief, it is also effective if a ventricular tachycardia occurs in such circumstances (*see* below)

The dosage varies widely in different cases We recommend 1 mg. digoxin by mouth as initial dose, followed by 0 25 mgm at six-hourly intervals, the patient being kept under careful observation for change in rhythm and signs of digitalis overdosage (p. 477) Instead of digoxin, digitoxin may be used, 0·1 mg. of digitoxin being equivalent to 0 25 mgm of

digoxin If intravenous injections are resorted to, we recommend 0·5 mgm digoxin in 10·0 cc., followed by 0 25 mgm at six-hourly intervals given by mouth. Oral digitalization can be started at the time of the injection. Instead of the intravenous injection of digoxin that of 0·25 mgm strophanthin may be given, followed by the same dose after twelve hours if no untoward effects occur; oral digitalization should be started at the same time (0 5 *mgm. digoxin as initial dose, followed by 0 25 mgm at six-hourly intervals). Strophanthin* should never be given if the patient had received digitalis within the preceding ten days and we do not recommend to exceed the doses stated

Magnesium sulphate. This has proved useful in doses of 15 0—20 0 cc. of a 20-per-cent. solution, given intravenously, in supraventricular and ventricular tachycardias (Boyd and Scherf)

Other drugs will be discussed only shortly since their effect is either not convincing or they cause unpleasant side-effects.

Choline and derivatives may be mentioned in the first place Of these, acetylcholine (Schliephake; Boden and Wankell, Abbott; Segers *et al*) and particularly acetyl-beta-methylcholine (Starr; Morgan) were used, but in view of the unpleasant side effects this treatment is now used only rarely. Acetyl-beta-methylcholine is given hypodermically in doses of 10–30 mgm (20–50 mgm, Morgan) A syringe for the intravenous injection of atropine (grain 1/50) should always be ready as antidote. For further details, the reader is referred to the papers by Starr and by Morgan

Similarly, prostigmine methylsulphate (0 5–1·0 mgm) (Battro *et al*) or neostigmine (1 mgm , Waldman and Pelner), both given intravenously, have been recommended. These drugs too, produce undesirable side-effects

Other drugs which have been recommended, but the use of which we should like to discourage, are epinephrine, atabrine, fagarine and calcium salts The intramuscular injection of paredrine hydrobromide (20 mgm., Griffith) or the intravenous injection of neo-synephrine (0·5 mgm) seem less risky, but in view of the possible considerable rise in blood pressure precipitated by the latter (Youmans *et al.*) we do not recommend their use.

The efficacy of procaine amide (Pronestyl) in the treatment of auricular paroxysmal tachycardia is not yet established and, while it seems promising to a certain extent, we should like to await further reports before expressing an opinion.

Further particulars about most of the drugs mentioned will be found in the appropriate sections of the chapter on " Drugs "

In conclusion we would advocate a healthy scepticism against any new drugs recommended for the treatment of paroxysmal tachycardia.

All these remarks about treatment apply only to supraventricular paroxysmal tachycardia without A-V block. The variety with block is far more difficult to treat The response of such patients to carotid sinus pressure, quinidine or digitalis is often poor and transient The most effective therapeutic measures have to be established in each case by trial and error.

Similar difficulties are experienced in the treatment of extrasystolie à paroxysmes tachycardiques, as already referred to.

Ventricular Paroxysmal Tachycardia

It is universally recognized that this variety of paroxysmal tachycardia carries a far more serious prognosis than the supraventricular type, since it is mostly associated with structural heart disease and is a dreaded complication of myocardial infarction. While every effort
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et al. had no heart
e syndrome made

the evaluation of the type of arrhythmia and its significance doubtful Reports of single cases of this kind are those of Stein and Driscoll, and of Mahaim and Perusset. The rôle played by digitalis overdosage in the production of this arrhythmia must not be forgotten

Regarding treatment, all the measures based on reflexes, which were discussed in connexion with supraventricular tachycardia, are ineffective with rare exceptions The drug of choice is quinidine In many cases oral medication is effective. We recommend 0·2 gramme as initial dose and, if no untoward effects occur, 0·4 gramme can be given every 2–3 hours If the arrhythmia persists after six hours the single dose can be increased to 0·6 gramme In exceptional cases much larger doses have been given, for example the maximum single dose employed by Armbrust *et al* being 2·5 grammes! If, however, the ventricular tachycardia occurred in association with myocardial infarction and is not terminated within six hours, the intravenous injection of quinidine in doses varying between 0·2 and 0·3 gramme is indicated and justified: the risk inherent in the arrhythmia in such circumstances outweighs the risk of the intravenous injection This method may, however, be superseded by procaine amide (Pronestyl), which has recently been introduced and has proved most successful in the treatment of this dangerous condition; in some cases it was superior to quinidine The doses recommended on the grounds of observations so far available are If given by mouth, 1·25 grammes as initial dose, followed in one hour by an additional 0·75 gramme if the tachycardia persists In the majority of cases this proved adequate to terminate the tachycardia, but if necessary subsequent doses of 0·5–1·0 gramme at two-hourly intervals may eliminate the arrhythmia When given intravenously the drug should be injected very slowly, the maximum rate being 100 mgm per minute or less, the dose varied in different cases between 200 and 1,000 mgm (that is, between 2 and 10 cc of the Pronestyl solution as supplied by the manufacturers) Continual observation of blood pressure and electrocardiogram during the injection is necessary with the intravenous route, and the injection should be discontinued immediately if a more pronounced fall in blood pressure occurs or the arrhythmia stops (*See also* section on "Cocaine")

Gonzalez Sabathie reported good effects in nine out of ten cases from the intravenous injection of 0·01 to 0·04 gramme of morphine

and our observations are in accordance with that of those authors We may summarize our views on this subject by stating that in ventricular tachycardia, provided the arrhythmia is not due to digitalis, this drug, if otherwise indicated, can be given far more freely than hitherto assumed and that in such cases it often abolishes the disturbance of rhythm

SUMMARY

The close relation between paroxysmal tachycardia and extrasystoles is emphasized and while a detailed description of the countless varieties of this arrhythmia is considered outside the scope of this book some special types are briefly discussed, namely. tachycardie à

pulses arising in a circumscribed ectopic focus and not due to a circus movement The mode of origin of paroxysmal tachycardia is thus assumed to be essentially the same as that of extrasystoles Some points presenting special difficulties in the differential diagnosis between

paroxysmal tachycardia and auricular flutter, and between supraventricular, atrio-ventricular and ventricular paroxysmal tachycardia are briefly discussed.

The treatment is discussed in some detail under the following headings:

Supraventricular paroxysmal tachycardia It is pointed out that such paroxysms can be terminated by way of reflex in a considerable proportion of cases; such reflexes are reviewed. Drug treatment should only be resorted to after such procedures had been given a fair trial. Amongst the great number of drugs which have been reported as sometimes successful, in practice only three can be recommended. quinidine, digitalis, and magnesium sulphate, in this order Details of dosage and administration are given. Other drugs are briefly mentioned, though not recommended.

Ventricular paroxysmal tachycardia The treatment of choice is quinidine, but procaine amide (Pronestyl), recently introduced, may to a certain extent replace quinidine in the treatment of this arrhythmia, particularly if it occurs as a complication of myocardial infarction, and in instances in which intravenous injections of quinidine were considered indicated hitherto Details of dosage and administration of these drugs are given Digitalis, which is usually thought to be contra-indicated in this arrhythmia, can in our opinion be given far more freely than hitherto assumed, provided the arrhythmia is not due to the drug, in such cases it often abolishes the arrhythmia

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CHAPTER VII

EXTRASYSTOLES AND THE NERVOUS SYSTEM

INTRODUCTORY REMARKS

The part which the nervous system plays in precipitating or modifying ectopic arrhythmias is as important as it is complex. Using the words " nervous system " in their widest sense, that is to include the action of autonomic nerves, reflexes, the central nervous system as well as psychological factors, its influence on such arrhythmias in man is so widespread and profound that the resulting clinical importance is obvious Moreover, a great deal of experimental evidence on this problem in various animals has been collected under widely varying conditions Taken together, such clinical and experimental observations throw some light on the mechanism of extrasystolic and allied arrhythmias and are thus also of physiological interest

The relationship between the nervous system and cardiac arrhythmias had been noticed for a long time, and its significance was grossly overrated in the past by some who considered such arrhythmias to be due only to nervous influence The observations that ectopic arrhythmias may occur in the isolated perfused heart and thus independent from central nervous control, that electrical stimulation of vagus or sympathetic nerves alone produces such irregularities only exceptionally whilst the opposite effects on the cardiac rhythm may result from the same kind of stimulation of the same nerve according to the conditions of the experiment, demonstrate conclusively that no simple relationship obtains It will be seen that in most cases, in which nervous influences precipitated extrasystolic and allied arrhythmias with any degree of certainty, complex experimental conditions were present which resulted in the heart's being predisposed to the exhibition of the arrhythmia It seems reasonable to postulate a similar predisposition in man to account for the widely varying incidence of such arrhythmias under seemingly similar conditions

ECTOPIC BEATS PRECIPITATED BY DIRECT (FARADIC) STIMULATION OF VAGUS AND SYMPATHETIC

While it was found that occasionally stimulation of the vagus alone (Hering 1909, Lewis 1914a) or sympathetic alone (Rothberger and Winterberg 1911a, p 344, 1911b, p 520 footnote, Kuré 1913) may elicit ectopic beats, this occurrence is exceptional and it soon became obvious that, in order for the stimulation of such autonomic nerves to produce ectopic rhythms, other conditions present at the same time had to render the heart predisposed for the development of arrhythmias of this kind.

One of the earliest of such observations is that of Hering (1901): If, in the isolated heart preparation, a sudden rise of intra-ventricular pressure, precipitated by clamping of the

reappear by vagal stimulation It is important to note that in some of these experiments the

extrasystoles occurred without any noticeable vagal slowing of the normal rate; it is clear, therefore, that the effect of vagal stimulation cannot consist exclusively in the retardation of the normal impulse formation, allowing more time for ectopic beats to become manifest. The further observation of Weiland's that only weak stimulation of the vagus precipitated extrasystoles, whereas strong stimuli had the reverse effect, points in the same direction. (*See also* Luten below) Hering (1911) emphasized the physiological significance of the fact that the occurrence of extrasystoles was independent of a change of the normal rate

In discussing these observations we have used the term " extrasystoles " for the heterotopic beats, in accordance with the authors of the papers discussed. However, the question arises whether heterotopic beats of this kind should be considered extrasystoles in the strict sense of the term The nature of extrasystoles and the difference between extrasystoles and automatic beats is discussed in the chapter on " Mechanism ", reasons will there be advanced for our view that those ectopic beats, which are not preceded by a precipitating beat at constant time intervals, are produced by a different mechanism and should therefore be distinguished as automatic beats from the more passive phenomenon of the true extrasystole

Similar considerations will have to be applied to the extensive investigations by Rothberger and Winterberg, where a more accurate determination about the origin and nature of the ectopic rhythm is possible since, in addition to the mechanical records of auricle and ventricle, electrocardiograms were also obtained In their experiments on dogs these authors found that simultaneous stimulation of vagus and sympathetic precipitated beats originating in distal centres in the ventricles Stimulation of the accelerans tended to precipitate impulse formation in the ipsilateral ventricle, when, at the same time, normal impulse formation was inhibited by vagal stimulation In these experiments stimulation of the right vagus usually had a more marked inhibitory effect on the normal pacemaker than that of the left (1911a) Ectopic beats occurred more readily if the animal had previously been given small doses of barium chloride (0 005–0 01 g); with larger doses (0 025–0 05 g) such arrhythmias occurred after stimulation of the left accelerans without simultaneous vagal stimulation (1911b) Calcium chloride had a similar effect, though much larger doses (0 1–0 2 g.) were necessary, but strontium and magnesium were ineffective It was also found that barium chloride did not lower the threshold for stimulation of the accelerans, and it was concluded that barium and calcium chloride had a selective sensitizing effect on the impulse-forming centres in the ventricles, an impressive early example of a predisposition of the heart to develop ectopic rhythms as a result of nervous influence. Other instances will be detailed below In Rothberger and Winterberg's records the ectopic beats occurred *in groups, without any definite time relationship to the preceding beat, normal or ectopic* By diminishing the intensity and particularly the duration of the electrical stimulation it was possible occasionally to precipitate single " extrasystoles " The arrhythmias observed in such experiments would, in our opinion, more appropriately be considered to be due to increased automatism of a ventricular centre or centres than to consist of extrasystoles Lewis (1914b) had already expressed doubts whether the arrhythmias experimentally produced by Rothberger and Winterberg and extrasystoles have the same genetic origin, and subsequent work has tended to substantiate such doubts.

In a similar manner, chloroform (Levy) and cyclopropane (Allen, Stutzman and Meek) were found to sensitize the heart in such a manner that subsequent stimulation of the sympathetic elicited ectopic arrhythmias The latter drug seems to have predisposed the heart to various arrhythmias on manipulation of the vagus though extrasystoles were observed in only three out of thirty-six operations (Freeman). During operations involving section or isolation of the gastric vagi premature beats were found only rarely in clinical and experimental (dogs) observations (Gullickson, McRae and Campbell) This will be discussed in the appropriate sections of the chapter on "Drugs" (pp 301, 304)

There can be no doubt, however, that true extrasystolic arrhythmias were produced by vagal stimulation in dogs after aconitine administration (Scherf, 1929) In these experiments an amorphous preparation was used (0 5 or 1·0 g in 100 cc. of distilled water, acidified) and the degree of intoxication carefully adjusted individually in each experiment If such small doses were employed that alone failed to produce any noticeable change in the rate or rhythm of the heart, faradic stimulation of the vagus, right or left, invariably produced a bigeminal rhythm or multiple extrasystoles arising in the same focus The extrasystoles usually were ventricular in origin, arising in the left ventricle more frequently than in the right, they started immediately with the vagal stimulation The extrasystoles of the bigemini were accurately coupled to the preceding beats and had constant shape in the electrocardiogram

Fig 156 provides an example of such an experiment The right vagus was stimulated by a weak faradic current after the first normal beat occurred Each automatic (escaped) beat occurring during vagal stimulation was followed by a group of four ventricular extrasystoles, the first of which was accurately coupled to the automatic beat (coupling 0 32 second) The extrasystoles persisted after the end of vagal stimulation for various periods of time, in some experiments for several hours, depending, amongst other conditions of the experiment, on the degree of aconitine intoxication If the extrasystoles had subsided, renewed vagal stimulation caused them to recommence If extrasystoles were already present as a result of the administration of aconitine, stimulation of the vagus invariably increased their number and precipitated multiple extrasystoles or short runs of paroxysmal tachycardia Atropine abolished the extrasystoles in certain stages of aconitine intoxication Choline and choline derivatives as well as potassium chloride had the same effect as vagal stimulation, choline remaining effective even with full atropinization

Conversely, short faradic stimulation of the sympathetic (accelerans) or, as unpublished experiments showed, injection of small doses of adrenaline abolished the extrasystoles after a short latent interval and at a time before the ensuing tachycardia would itself be likely to have this result Calcium chloride (1–5 cc of a 10-per cent solution) had a similar effect.

In a minority of the experiments auricular extrasystoles occurred, at times as auricular bigemini Vagal stimulation had essentially the same effect on auricular as on ventricular extrasystoles, with the important difference that, whereas the ventricular extrasystoles occurred immediately at the onset of vagal stimulation, the auricular ones did so shortly after the end of stimulation, if auricular extrasystoles were present as the result of aconitine alone, they temporarily disappeared during vagal stimulation, reappearing in increased numbers shortly after the end of stimulation During vagal stimulation the inhibitory

common in man, can only with great difficulty be produced in animals The few other methods known to produce this form of bigeminal action are discussed on p 194 The importance of being able to study in experiments an arrhythmia which is such a frequent

recent observation (Scherf and Chick) that the topical application of acetylcholine to the

ectopic rhythms

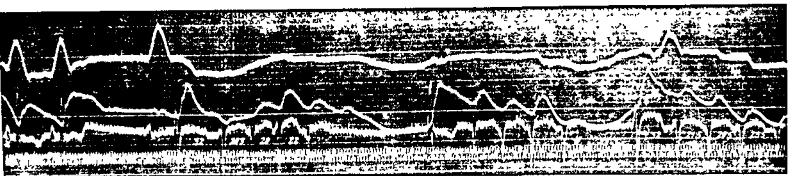


Fig 156—From an experiment on a dog Records from above downward suspension record of right auricle, of right ventricle, electrocardiogram (ano-oesophageal lead), time base 0 02 second Stimulation of the right vagus precipitates multiple ventricular extrasystoles after sensitization with aconitine The beginning of the (faradic) stimulation is recognizable in the figure (in the second P wave) by the slight distortion of the electrocardiogram produced by the faradic current From Scherf 1929, *Z ges exp Med*

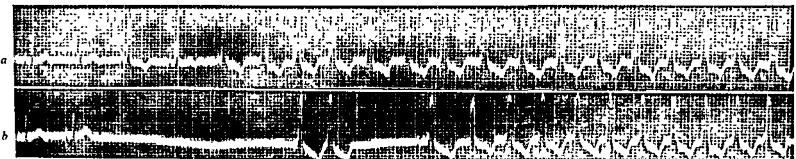


Fig 157—From an experiment on a dog Top record, regular ventricular tachycardia elicited by the topical application of a 30 per cent solution of sodium chloride on the right ventricle Bottom record Ventricular tachycardia precipitated by vagal stimulation. The bottom record was obtained after the top record For further explanation, see text From Piccione and Scherf *Bull N.Y med. Coll*

It is also significant that in those particular experimental conditions vagal stimulation had the effect of enhancing ectopic impulse formation in the ventricles while having the usual inhibiting effect on the higher centres of impulse formation This opposite effect of stimulation of the same nerve on the various centres, also proved for the sympathetic, is of considerable physiological importance regarding the mechanism of impulse formation (*See* Scherf, 1929, also the chapter on " Mechanism of Origin of Extrasystoles ".) Furthermore, the sympathetic is known not only to have a direct effect on the mammalian ventricle, but there to facilitate the onset of ectopic rhythms, so that the described effect of stimulation of the sympathetic in abolishing extrasystoles is the reverse of that observed in many other experimental conditions. A further instance of this kind is the suppression, by sympathomimetic compounds given intravenously, of ventricular ectopic tachycardias elicited in dogs by the topical application of aconitine (Charlier and Klutz)

Ventricular ectopic beats were also elicited by vagal stimulation in dogs after injection of digitalis (Kobacker and Scherf) The rate of the ectopic rhythms appearing during and shortly after stimulation of the vagus was slightly higher than that of the prevailing sinus rhythm

That stimulation of the vagus on the one hand and of the sympathetic on the other need not always have the opposite effect in producing and abolishing, respectively, extrasystolic arrhythmias was shown by Piccione and Scherf in experiments on extrasystoles caused in the dog by the application of hypertonic solutions of sodium or barium chloride on the cardiac surface or by subepicardial injections. If tachycardias thus produced had subsided spontaneously, faradic stimulation of the sympathetic, particularly of the right stellate ganglion, brought them out again and their rate increased markedly But the abnormal beats also re-appeared if the vagus was stimulated. In some cases the latter phenomenon may simply have been due to the slowing of the normal rhythm which facilitated the occurrence of ectopic ventricular beats Not rarely, however, a ventricular tachycardia which had disappeared could be brought out again for a period of three to four minutes by stimulation of the right or left vagus, and on these occasions the rate of the tachycardia was faster than that produced by the previous chemical irritation alone without vagal stimulation This would appear to be another of the few instances pointing to a direct effect of the vagus on the mammalian ventricle

Fig 157 was obtained from such an experiment. A subpericardial injection of 0 1 cc of a 30 per cent solution of sodium chloride in the conus area of the right ventricle was followed by a ventricular tachycardia (Fig 157a) The rate of the sinus rhythm was 115 and that of the tachycardia was 162 Two minutes later the tachycardia had disappeared At this stage the right vagus was faradically stimulated (Fig 157b), with the effect that a prolonged standstill of the heart occurred, which was interrupted by two beats originating in the same area as the extrasystoles which followed the injection of sodium chloride After a second, shorter interval (stimulation of the vagus continuing), paroxysmal tachycardia with a rate of 180 and again originating in the same focus occurred Since, by repeating vagal stimulation after a few minutes, short bouts of the same tachycardia could be elicited again, the assumption seems reasonable that such spells of tachycardia were not a coincidence A short bigeminal rhythm also could be precipitated by vagal stimulation in some of these experiments.

In dogs, following the intravenous administration of thiobarbiturates, ventricular extrasystoles appeared during vagal stimulation even if they had been absent before (Gruber).

Fig 158 demonstrates two auricular extrasystoles, originating in different foci, following prolonged faradic stimulation of the right vagus in a dog anaesthetized with nembutal (without any other drug). The stimulation of the right vagus was repeated six times and one or two auricular extrasystoles appeared after each stimulation.

These examples illustrate how complex the action of stimulation of vagus and

sympathetic is in its effect on extrasystolic and allied arrhythmias. According to the circumstances of the experiment, the kind of animal and anaesthetic used, and the kind of drug employed in order to sensitize the centres of ectopic impulse formation, stimulation of the same nerve may have quite different and at times opposite effects. It is also evident that stimulation of the cardiac nerves alone produced extrasystolic and allied arrhythmias only in a small minority of cases and that in all those experiments, in which such arrhythmias followed stimulation of these nerves with any degree of certainty, the heart had been rendered in a special condition, predisposing it for the development of ectopic arrhythmias

At this juncture the fact should be stressed that results obtained in experiments on rabbits should only be used with special reserve for the analysis of the mechanism of such arrhythmias in other animals and man, since ectopic arrhythmias are apt to occur especially easily in the rabbit, particularly if morphine, *which is known to favour their occurrence*, was used as an anaesthetic (Kuré, 1913, Hering, 1915)

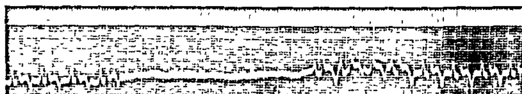


FIG 158 —From an experiment on a dog Two auricular extrasystoles following prolonged faradic stimulation of the right vagus

ECTOPIC BEATS PRECIPITATED BY WAY OF REFLEX FROM THE CAROTID SINUS AND THE PART PLAYED BY THE PRESSO-RECEPTOR NERVES

Some relevant observations, dating from long before the discovery of the function of the carotid sinus and of the action of presso-receptor nerves, may briefly be quoted Thus Cyon (quoted from Koch) found in 1898 that stimulation of the depressor nerve abolished bigeminal heart action even if the lowering of blood pressure was negligible This was subsequently confirmed by Hering (1922) Irregular heart action in rabbits as a result of clamping the carotid arteries was reported by Sewall and Steiner as early as 1885, and later by Hirsch and Stadler with experimentally produced aortic incompetence after severing of the depressor nerves Kisch, who studied such arrhythmias more closely using, however, only a record of the blood pressure for their analysis, interpreted them as extrasystoles and found that their occurrence was facilitated by simultaneous dyspnoea, stimulation of the central end of the vagus or of the superior laryngeal nerve, and that they persisted after bilateral vagotomy or atropinization A better understanding of the mechanism of such arrhythmias became possible only after the discovery by Hering of the carotid sinus as a site of origin of reflexes Hering (1927) himself added the observation that stimulation of the carotid nerve abolished arrhythmias produced by clamping the carotid arteries and that, just as in the case of the depressor nerve, this effect was independent of a change in blood pressure Heymans (1929), (quoted from Regniers, 1930), noticed the occurrence of extrasystoles when the pressure in the carotid sinus fell to 70–80 mm Hg

Such arrhythmias elicited by clamping of the carotid arteries were subsequently studied by means of electrocardiograms. Regniers found that ectopic beats occurred singly as well as in groups, that they originated from various foci, and that paroxysmal tachycardia as well [illegible] He confirmed that such arrhyth- [illegible] ergotamine. [illegible] the carotid [illegible]

arteries occurred more readily if the animals had been sensitized with barium chloride, aconitine or strophantin, given in doses which alone did not produce any changes in heart rate or rhythm In some experiments with barium long chains of bigeminal heart action with constant coupling and constant shape of the extrasystoles in the electrocardiogram could be produced (Fig 159), the arrhythmia immediately disappearing on releasing the carotids, to reappear on renewed clamping—another of the few methods experimentally to produce this arrhythmia Severing of both depressor nerves facilitated the occurrence of arrhythmias resulting from clamping of the carotid arteries (Hering, 1925, Regniers, 1929, Schott) This was to be expected in view of the synergistic action of depressor and carotid sinus nerves By removing their compensating action severing of the depressor nerves will enhance the effect of reducing the physiological stimulus of the carotid sinus nerves which results from clamping of the common carotid arteries In such experiments it was also found that stimulation of the intact vagus may precipitate the occurrence of extrasystoles as well as abolish them (Schott) Similarly, Danielopolu, Marcou and Proca reported that stimulation of the carotid sinus in dogs or cats, sensitized by means of ligatures in the myocardium or of small branches of the coronary arteries, or by means of intravenous injections

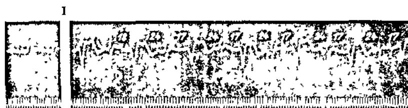


Fig 159 [illegible]

of calcium or barium chloride or strophanthin, may precipitate as well as abolish ectopic rhythms Dikshit (1934b) found in cats that sodium barbitone given intracerebrally or intravenously lessened or abolished cardiac arrhythmias elicited by clamping of the carotid arteries

It can therefore be said that stimulation of the presso-receptor nerves tends on the whole to prevent or abolish ectopic rhythms whereas elimination of their action (severing of the depressor and/or sinus nerves, lowering of the pressure in the sinus by clamping the common carotid arteries) has the opposite effect It must be borne in mind, however, that the reverse of this usual effect may be observed, depending, *inter alia*, on the rhythm prevailing at the time of the experimental interference on such nerves

These experimental findings accord well with the observations that pressure on the carotid sinus in man may precipitate as well as abolish ectopic beats Rihl (1912) found that pressure on the " vagus " elicited " extrasystoles ", but as he used only mechanical records, [illegible]

extrasystoles which in the electrocardiogram had the same or almost the same shape as those occurring spontaneously In both, extrasystoles had started as a result of digitalis, but in one of them no digitalis had been given for ten days Digitalis extrasystoles with fixed

coupling, but arising from various foci, produced by "vagal" pressure and not associated with any material change in the auricular rate had been described previously by Weil.

Fig. 160a shows a ventricular extrasystole which occurred during carotid sinus pressure applied for terminating an attack of auricular paroxysmal tachycardia. Observations of this kind are fairly common.

Not only single, but also multiple ventricular ectopic beats may occur during carotid sinus pressure Fig. 160b provides an example obtained in a fifty-four-year-old woman complaining of palpitation The tracing shows right bundle branch block; as a result of pressure on the right carotid sinus multiple ventricular ectopic beats were recorded and this observation could be repeated at short intervals. It was made in the same patient whose record is reproduced in Wenckebach and Winterberg's monograph (Fig 190 on plate 80), and it was also observed that pressure on the right "vagus" precipitated a ventricular tachycardia with a rate up to 278 which, moreover, could be abolished by the same manoeuvre which elicited it

Meredith and Beckwith reported two cases in which ventricular tachycardia was recorded during carotid sinus pressure applied for stopping an attack of paroxysmal supraventricular tachycardia.

The observation, quoted earlier in this chapter, that topical application of acetylcholine may precipitate ectopic ventricular rhythms in the dog may well have a bearing on the mode of origin of such ectopic arrhythmias occurring during carotid sinus pressure.

Regarding such arrhythmias arising in the *auricles*, auricular extrasystoles, paroxysmal auricular tachycardia, auricular flutter and fibrillation have been described following carotid sinus pressure (Aalsmeer, Mandelstamm; Blumenfeld, Schaeffeler and Zullo). Fig 160c shows two ectopic auricular beats which were recorded during pressure on the right carotid sinus applied to terminate an attack of supraventricular tachycardia

On the other hand, carotid sinus pressure may also suppress extrasystoles. This is easily understood in the case of *auricular* ones, as impulse formation in the auricles is known to be largely under vagal control Thus Luten reported a carefully analysed case in which auricular extrasystoles disappeared soon after injection of atropine (grain 1/30) at a time when the sinus rate was slowed as a result of the initial vagal stimulation. With the subsequent tachycardia in the vago-paralytic stage of the atropine effect, the ectopic beats became more and more numerous Apart from the effect of atropine the extrasystoles disappeared as a result of "vagal" pressure, but the effect was not constant. This observation demonstrates that, at least in some cases, vagal tone is a far more important factor in determining the occurrence of extrasystoles than the length of the diastolic interval.

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neck was assumed to produce a direct mechanical stimulation of the vagus As it is now known that stimulation of the presso-receptor nerves results not only in an increase of vagal, but also in a decrease of sympathetic tone, this latter effect may reasonably be assumed to be the cause of the disappearance of ventricular extrasystoles as a result of carotid sinus pressure. The paramount importance of efferent sympathetic pathways in such reflexes has been demonstrated in a great variety of experimental conditions By recording in cats the sympathetic impulses in one of the small nerves running from the stellate ganglion to the heart, Bronk, Ferguson and Solandt found that increase in the pressure within the carotid sinus results in a decrease of the sympathetic impulses, amounting to temporary complete inhibition if the pressure was raised to 125–150 mm. Hg The duration of this inhibition depended on the height of the pressure in the sinus and was often increased by section of both the aortic depressor nerves.

The effect of direct mechanical stimulation, by pinching with a pair of forceps, of the

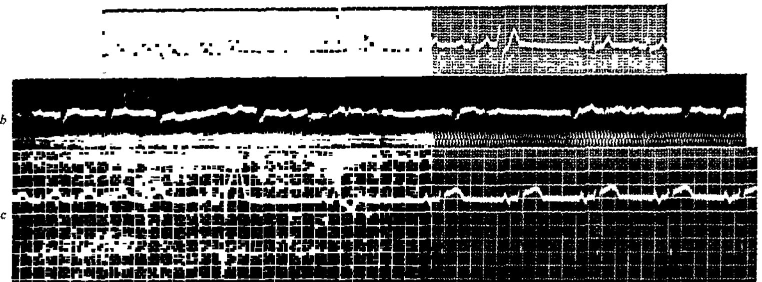


FIG 160—*a* A ventricular extrasystole occurring during carotid sinus pressure which terminates an attack of paroxysmal auricular tachycardia *b* Lead I Multiple ventricular ectopic beats during carotid sinus pressure The two records were obtained from different patients *c* Lead V-1 Two ectopic auricular beats with aberrant intra-ventricular conduction, recorded during pressure on the right carotid sinus. Note the difference in shape of the P waves of these two beats, indicating either different site of origin or intra-auricular disturbances of conduction Both differ from the di-phasic P waves of the subsequent sinus beats

carotid sinus in man was studied by Hill in twenty patients in whom the region was exposed for operation Only in the two cases in which chloroform was used as anaesthetic were ventricular extrasystoles recorded, here they tended to occur as bigemini, the extrasystoles being only slightly premature The arrhythmia was not accompanied by a significant variation in the heart rate and closely resembled that arising spontaneously under chloroform anaesthesia

It is thus obvious that carotid sinus pressure in man may precipitate as well as abolish extrasystoles. Hering (1925) pointed out that this seemingly contradictory result may be due to the exact site at which the pressure is applied: if the sinus itself is compressed it results in a stimulation of the sinus nerve via the mechanical stimulation of the carotid sinus

admitted that such a sharp distinction between the two points of compression often is not possible; with compression below the sinus a mechanical effect may be produced on the sinus by traction, and in subjects with short and obese necks it may be altogether impossible accurately to localize the site of pressure While in the clinical experiment the exact site of the pressure is, of course, of importance, no such considerations arise in connexion with animal experiments In our view the observation that the same procedure may have the opposite effect on the heart rhythm is only one of many similar instances, well known in

of nerves depends *inter alia*

gal stimulation was found to be dependent only on the condition of the organ, the atonic stomach responded by contraction, the hypertonic one by relaxation (McSwiney and Wadge) Similar conditions were found by McCrea and McSwiney regarding the effect, upon the pylorus and fundus of the cat's stomach, of stimulation of the hepatic branch of the vagus The effect upon the uterus of stimulation of the hypogastric nerve differs according to the presence or absence of pregnancy (Langley and Anderson)

Regarding the effect of nervous stimulation by way of reflex: independent of the site of stimulation the excitation tends to favour stretched muscles (v Uexkull, Sherrington, Magnus) and is thus dependent on the conditions in the periphery (Bethe) In decerebrate cats pressure on the hard palate produces, by way of reflex, opening of the jaws if the mouth was shut, but their clenching if the mouth was open In man a flexor reflex can in certain circumstances, depending on the situation as a whole, be converted into an extensor one (Bethe and Fischer) (For ref of the papers quoted in the last two paragraphs, see Schott)

It seems to us that the condition of the heart and particularly its rhythm at the time is one of the main factors determining whether stimulation of the presso-receptor nerves results in precipitating or abolishing ectopic arrhythmias

In a similar way as with carotid sinus pressure, extrasystoles were occasionally seen during or following pressure on the eye bulb (Aschner-Dagnini reflex), (Jenny; Ferralis and Pezzi; Danielopolu *et al*, 1925). Pruche stated, however, that he found extrasystoles only in cases in which they had been present before ocular pressure was applied. Sabena and Posteli examined electrocardiographically the effect of ocular pressure in fifty patients and, amongst other variations in heart rate and rhythm, found extrasystoles of several kinds, namely auricular, ventricular and polymorphic No tracings are, however, reproduced in their paper. Landman and Ehrenfeld reported an observation in which eyeball pressure was thought to have precipitated short runs of ventricular fibrillation, but in our opinion the reproduced tracings demonstrate short paroxysms of multiform ventricular extrasystoles

Roth reported an observation on an eighteen-year-old man with angioneurotic oedema, in which ocular pressure produced extrasystoles if adrenaline (1 mg.) had been injected previously. The analogy of this clinical observation with the experimental findings of Rothberger and Winterberg, that combined stimulation of vagus and sympathetic may produce ectopic arrhythmias, is obvious

ECTOPIC BEATS DUE TO REFLEXES FROM THE RESPIRATORY TRACT

Cardiac arrhythmias resulting by way of reflex from chemical irritation of the nasal mucous membrane have been known since Kratschmer's investigations on rabbits in 1870. Using a variety of chemical irritants, amongst them chloroform, ammonia and tobacco

affect the arrhythmias, but section of the trigeminal abolished them

Much of this early work has subsequently been confirmed and amplified Knoll (1872), studying in detail the *pulsus bigeminus* under the conditions in which Kratschmer found it to occur, observed that its duration equalled that of two normal cycles, a finding that should later prove of such decisive importance for the accurate analysis of extrasystolic arrhythmias. He also clearly recognized that the *pulsus bigeminus* and *trigeminus* were caused by

curred independently of a rise in blood pressure and confirmed that they persisted after bilateral vagotomy, atropinization and removal of the lower cervical and upper dorsal gangia. The methods available at that time were inadequate for a reliable analysis of the kind of arrhythmia, but in view of subsequent observations the assumption seems well justified that they consisted largely of ectopic arrhythmias and extrasystoles, as stated by Hering (1900, 1901)

Koblanck and Roeder, starting from Koblanck's observation that arrhythmias could be elicited in man by stimulation of certain areas in the nose, investigated this problem in dogs and rabbits It was found that arrhythmias could be produced by stimulation of a circumscribed area on the posterior part of the nasal septum opposite the middle turbinate,

inadequate that it was repeatedly criticized

Magne, Mayer and Plantefol also found arrhythmias and bradycardia resulting from

As far as the bradycardia is concerned which occurs in rabbits as a result of the insufflation of irritating vapours into the nostrils, Brucke conclusively demonstrated in 1917 that the efferent mechanism consists not only of a stimulation of the vagi, but also—at least in certain animals—of an additional inhibition of the sympathetics.

More recently this problem was extensively re-investigated by Allen (1930–33) Arrhythmias (*pulsus bigeminus*) were found to result in rabbits particularly easily from insufflation of benzol and could also be produced by stimulation of the central end of the cut vagus, but not by faradic or mechanical stimulation of the peripheral end of vagus, depressor and cervical sympathetic, or of the lateral wall of the nostrils. No constant relationship between the onset of bigeminal pulse and height of blood pressure was found, and the arrhythmias occurred even if a rise in blood pressure was prevented by an equalizer, by ergotamine or transection of the spinal cord in the midthoracic region; they were also independent of the carotid sinuses (1930b) The afferent pathway was found to be the trigeminal though the olfactory nerves may also have some part (1930a) The impulses descend the median half of the lateral columns of the spinal cord and pass to the left ventricle by way of the upper thoracic roots and the stellate ganglia (1931a) The arrhythmias were abolished by section of the lower cervical cord or removal of the stellate ganglia. The central connexions of this reflex are discussed below (p 267) While it seems fairly certain that the arrhythmias studied by Allen were extrasystolic in origin, only very few electrocardiograms are reproduced and the diagnosis of the disturbances of rhythm is mainly based on carotid blood pressure tracings No finer analysis of the arrhythmias is therefore possible, in particular no conclusions can be drawn about the focus of origin of the ectopic beats. Owing to the inertia of the recording system employed not even a tentative explanation can be given of the nature of changes in the arrhythmia which were observed in some experiments. Moreover, the results about the relationship between rise of blood pressure and onset of premature beats were inconclusive

A few words here may not be amiss to clarify our attitude toward work on arrhythmias in which only mechanical records of blood pressure and/or arterial pulse tracings were obtained Much is owed to work of this kind which showed under what conditions arrhythmias occur and by what interferences they are modified, prevented or abolished. The presence of ectopic beats and extrasystoles may be inferred from such records with a certain degree of probability, particularly if additional mechanical tracings of auricular activity or preferably electrocardiograms were recorded in at least a certain proportion of experiments. We should like to emphasize, however, that no reliable analysis of the underlying arrhythmias is possible on the strength of arterial pulse or blood-pressure tracings, as these fail to give any information about auricular activity which is indispensable for analysis A great variety of mechanisms may, for instance, result in a *bigeminal pulse*, as is discussed in the appropriate chapter (p 204) Moreover, with a mechanical pulse tracing or the usual blood-pressure record the inertia of the recording system results in such marked distortions of the record in shape and in time that not even the fundamental distinction between disturbances of impulse formation (ectopic beats, extrasystoles) and disturbances of conduction can be made In order accurately to analyse arrhythmias, either electrocardiograms or records of ventricular *and* auricular activity obtained with adequate recording systems, or both, have to be postulated For these reasons the value of some otherwise important work is limited if a detailed analysis of the arrhythmias is the object in view

While, as already mentioned, Magne, Mayer and Plantefol failed to find any cardiac
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corded, the latter sometimes arising from various foci A possible anatomical basis for
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marked slowing of the
These findings are of

practical importance as they demonstrate the need for caution in applying mechanical stimuli to the trachea or bronchi especially in light anaesthesia, cyclopropane seems particularly apt to sensitize the heart in this respect.

Amongst the arrhythmias complicating total pneumonectomy extrasystoles formed only a small fraction (Massie and Valle).

Regarding the effect of respiration on the incidence of extrasystoles, Busquet observed in the dog that they were more frequent during expiration and attributed this to the slower heart rate Owing to the rather primitive method used no more detailed analysis of the arrhythmia is possible.

Ventricular and auricular extrasystoles as well as auricular flutter and fibrillation precipitated by *deep breathing* have been repeatedly described (Stokes; Smith and Moody, Burak and Scherf). Evans investigated the effect of deep inbreathing on lead 3 in two hundred healthy adults and found that in one case deep inspiration always induced a short bout of paroxysmal tachycardia; in five instances extrasystoles appeared with deep inspiration while in three they disappeared, having been present in lead 3 taken during ordinary respiration In Case 3 of the series of Smith and Moody deep breathing caused paroxysmal auricular fibrillation only when the patient was apprehensive, whereas, after his fears had been dispelled, deep breathing produced only extrasystoles, an interesting example showing the interaction of several predisposing factors in producing various arrhythmias. In another of their cases (Case 2) return extrasystoles followed deep breathing

Extrasystoles occurring as a result of forced expiration against the closed glottis (Valsalva's experiment) are at least partly due to reflexes Thus Burger found extrasystoles, following the rise in intrapulmonary pressure thus produced, in fifteen amongst 145 subjects and attributed these and other changes in the electrocardiogram to a vagal effect which, under such conditions, outlasts the increase in sympathetic tone after the end of the effort.

Forssman and Stenqvist reported an unusual observation in a man of thirty-six without cardiac disease This individual was able to produce attacks of paroxysmal tachycardia by deep inspiration, by pushing forward his abdominal wall without straining and while holding his breath, and subsequently also by Valsalva's experiment Carotid sinus pressure, ergotamine tartrate or prostigmine had no effect on the tachycardia. As the result of quini-

ECTOPIC BEATS DUE TO REFLEXES FROM THE GASTRO-INTESTINAL TRACT

The effect, on the cardiac rate and rhythm, of reflexes originating in the gastro-intestinal tract has been known for a long time and in its extreme degree was demonstrated by Goltz's classic experiment on the frog in which he showed cardiac standstill to follow a blow on the abdomen Engelmann found in experiments on the effect, upon the frog's heart, of direct stimulation that subthreshold stimuli became effective as a result of faradic stimulation of stomach or intestines, which he attributed to a sensitization of the heart due to reflex vagal stimulation Clinically, the importance of gastro-intestinal maladies on the rhythm of the heart had, at certain times, if anything been overrated, reference has already been made to Solano's and Laennec's view that intermittent pulse was a sign of impending diarrhoea ("Historical Remarks")

accurately coupled), and sometimes nodal rhythm was found, and such attacks could be

precipitated by touching the left faucial pillars or the pharyngeal aspect of the tongue on the left The attacks were abolished by application of radium to the left tonsillar region. Extrasystoles and short attacks of paroxysmal tachycardia produced by swallowing were reported by Sakai and Mori, Wenckebach and Winterberg, Gallavardin and Froment (two cases), Forsberg. In this connexion reports of the occurrence of Adams-Stokes attacks due to swallowing are also relevant, as they not only show a reflex effect upon the heart rhythm of swallowing, but in some cases they were associated with ectopic impulse formation Thus Flaum and Klima reported a case of a sixty-three-year-old man in whom swallowing induced Adams-Stokes attacks, the electrocardiogram showed complete standstill up to 5 minutes 28 seconds, *interpreted as sino-auricular block. During the long intervals of standstill* automatic beats occurred, partly of A-V, partly of ventricular origin. Such attacks could invariably by produced by touching the superior laryngeal nerve in the left pyriform fossa or at its passage through the hyothyroid membrane, whereas carotid sinus pressure was without effect Reiniger, in discussing what appears the same case, mentioned that ventricular extrasystoles occurred before the attacks, disappeared during paroxysms, to reappear when the original rhythm was restored, the extrasystoles having various forms and varying coupling. Weiss and Ferris reported the occurrence of Adams-Stokes attacks on swallowing in a sixty-four-year-old man which originated from a traction diverticulum of the oesophagus; such attacks could be precipitated by distending the diverticulum by means of inflating a balloon inserted into it The electrocardiogram showed complete heart block during the attacks, epinephrine and ephedrine, while not preventing the block, so increased automatic impulse formation that a regular ventricular rhythm ensued, the rate of which was sufficiently high to prevent the onset of symptoms The afferent path of the reflex, at least in some of such cases, is believed to pass through the superior laryngeal nerve.

Arrhythmias following experimental distension of the stomach seem first to have been reported in 1872 by Mayer and Přibram, but were found only in a minority of the experiments. Subsequent studies confirmed that the occurrence of arrhythmias under such conditions is by no means constant and rather the exception Thus Burgess, Scott and Ivy found periodically recurring premature beats on distension of the stomach in only one out of twelve dogs, and Owen obtained extrasystoles only rarely upon distending the viscera in anaesthetized dogs Pearcy and Howard found extrasystoles on distension or squeezing of various viscera in dogs which were sensitized with barium or digitalis. In such experiments the anaesthetic employed and the kind of animal used are of paramount importance

In man the occurrence of extrasystoles after a heavy meal is a common occurrence and other conditions producing a displacement upwards of the diaphragms also frequently precipitate such arrhythmias, for example pregnancy

Kaestner reported numerous ventricular extrasystoles in a fifty-nine-year-old man with a hiatus hernia They invariably occurred immediately after assuming the supine position and then disappeared.

Clinical observations testify to the intimate relationship between gall-bladder and heart action. Here again, however, experimental investigations gave inconclusive results Schrager and Ivy saw " skipped beats " in only one out of five dogs on distending the biliary passages. According to Crittenden and Ivy icterus in unanaesthetized dogs seemed to facilitate the onset of cardiac arrhythmias, including ectopic beats, on distension of the biliary passages. The cardiac manifestations, however, were primarily associated with pain, vomiting or retching and were abolished by atropine.

In man reports of carefully investigated cases are few. Straus and Hamburger found [illegible]

temporarily in the same patient after each of two operations for duodenal ulcer and periduodenal adhesions respectively. In yet another case auricular extrasystoles and flutter became more marked after cholecystectomy. The authors emphasize that three out of those four patients were " neurotic ", another instance of several factors being present to sensitize the heart Another impressive example of the effect of a diseased gall-bladder on cardiac function is provided by the first case of a series of six, published by Fitz-Hugh and Wolferth In this patient, suffering from nocturnal pain in the precordium and left shoulder, in addition to violent attacks of epigastric and right upper quadrant pain, the electrocardiogram showed signs of myocardial damage with numerous ventricular extrasystoles, six weeks after cholecystectomy the tracing was entirely normal and the extrasystoles had disappeared

Reports about the occurrence of extrasystoles as a result of handling abdominal viscera at operations in man are conflicting Bettmann and Rubinfeld saw ectopic beats during cholecystectomy, performed under spinal anaesthesia, in only two out of sixteen patients Wakefield found extrasystoles frequently (together with other electrocardiographic changes) when traction was made on the gall-bladder or when it was distended with normal saline solution The effect of major abdominal operations on the cardiac rhythm was studied electrocardiographically by Maher and collaborators In eighty-nine operations (in which ether or nitrous oxide was used) extrasystoles were found in thirteen cases (auricular in five, ventricular in four, nodal in two and auricular and ventricular in two); only in ten instances was the occurrence of the arrhythmia related with certainty to a definite operative procedure, for example, stretching the mesentery, pulling the gall-bladder or omentum, or palpating a neoplasm

CENTRAL NERVOUS SYSTEM—BRAIN—AND ECTOPIC BEATS

A G Levy's extensive work on the occurrence of extrasystoles in cats under light chloroform anaesthesia was the starting point of important investigations demonstrating the part played by certain areas in the brain in the production of such arrhythmias Levy himself demonstrated that, when epinephrine was injected intravenously into cats under light chloroform anaesthesia, extrasystoles and ventricular fibrillation ensued within a few seconds and that this effect was still present in pithed cats with the brain destroyed

Stimulation of the central end of the vagus also may precipitate extrasystoles in cats under chloroform anaesthesia (Brow, Long, and Beattie, Dikshit, 1934a)

Further progress was made by the detailed investigations of Brow, Long and Beattie, starting from the chance discovery that such extrasystoles in lightly chloroformed cats were abolished or prevented by decerebration at the Sherrington level It was found that a centre or centres exist in a certain region in the brain stem, the removal of which resulted in the abolition of the extrasystoles, the area having the following boundaries anteriorly and superiorly, a line joining the anterior edge of the superior colliculi to the posterior edge of the optic chiasma, posteriorly, a line joining the anterior edge of the superior colliculi to the posterior edge of the mammilary bodies, laterally, an imaginary plane not more than 3 or 4 mm from the medial sagittal plane Stimulation of this region was found to produce extrasystoles when they were not already produced by chloroform Moreover, stimulation of certain points of the hypothalamus produced extrasystoles, one such point was close to the entrance of the aqueduct of Sylvius into the third ventricle, another one about 3 mm. above and slightly posterior to the origin of the infundibular recess Degeneration experi-

stimulation of the above region of the hypothalamus, was due to stimulation of the general sympathetic pathways as well as of the paths controlling the secretion of adrenaline, for it

was found that stimulation of the hypothalamus still produced extrasystoles after the removal of the suprarenals.

Blocking or interruption of afferent pathways of the carotid sinus caused extrasystoles which disappeared after cutting of adrenergic fibres which descend from the posterior hypothalamus (Miller)

In a certain proportion of experiments ectopic arrhythmias were observed after injection of 0 1–0·5γ of acetylcholine into the lateral ventricles (Dikshit, 1934a). Such irregularities could also be produced in cats by the intraventricular injection of caffeine and nicotine; sodium barbitone given intracerebrally or intravenously lessened or abolished such arrhythmias provoked by caffeine (Dikshit, 1934b). Dikshit concluded that caffeine can produce cardiac irregularities by some action on the hypothalamic centres

In unanaesthetized dogs intracerebral (ventricular) injection of strophanthin produced numerous extrasystoles, followed by ventricular tachycardia of about three hundred per minute Such arrhythmias were abolished by intravenous barbital, but not by vagotomy. This effect was specific for strophanthin; the only other substance which was found to have a somewhat similar, though considerably less marked, effect, was pitressin Histamine caused auricular, but never ventricular extrasystoles (Korth, Marx and Weinberg)

Allen (1931b) obtained in rabbits similar results regarding chemical or faradic stimulation of the hypothalamus in three animals premature systolic arrhythmias followed such stimulation (In the few instances in which arrhythmias were produced by strong faradic stimulation of the superior colliculi this was attributed to the concomitant marked rise in blood pressure, as no such arrhythmias occurred if the rise in blood pressure was kept below 5 mm. Hg) On the other hand, the arrhythmias produced by insufflation of benzol persisted after section of the brain in a plane similar to that which Brow and his collaborators found in cats to abolish chloroform extrasystoles Allen concluded that the pathway is through some connexion between the trigeminal and a centre below the diencephalon

A similar mechanism seems to have been present in the arrhythmias produced in dogs by intracisternal injection of potassium phosphate (a m/6 mixture of mono- and di-potassium phosphate of p_H 7·6) (Walker, Smolik and Gilson) The irregularities consisted in ventricular extrasystoles, at times occurring as bigeminal rhythm They were abolished by section of the cord at the level of the sixth cervical vertebra, though they could still be elicited by tetanic stimulation of the spinal cord just below the level of section or by stimulation of one or the other stellate ganglia, especially the left. They were not abolished by brain stem transection in the intercollicular or pontile region and were more pronounced after vagotomy. With intact vagi ectopic beats occurred more frequently during inspiration, when the heart rate was higher, and in the case of bigemini the coupling of the extrasystoles was constant even if respiratory arrhythmia was marked. It is considered possible that the arrhythmias were due to stimulation of cells in the floor of the fourth ventricle, causing excitation of pathways which descend in the spinal cord and leave in the sympathetic nerves at the upper thoracic levels Ectopic impulse formation was enhanced by the absence of vagal influence and was independent of the hypothalamus

Regarding ventricular tachycardia produced by adrenaline in dogs under cyclopropane anaesthesia, it was found that no such arrhythmia occurred in two dogs after a lesion in the pons at the level of the trigeminal nerve (Allen, Stutzman and Meek)

As far as the efferent pathways are concerned the stimulation of which produced, and the section of which prevented or abolished, ectopic arrhythmias due to chloroform, benzol or cyclopropane, the paramount importance of the sympathetic, that is, the *rami communicantes* of the upper thoracic segments and the stellate ganglia, has been established by the work on these subjects discussed in this chapter The above findings that stimulation of the posterior and lateral parts of the hypothalamus produces such arrhythmias accords well with these observations, since it is known that these parts of the hypothalamus contain

centres of vital importance for the activity of the sympathetic nervous system Contrariwise, vagal stimulation tends to prevent or abolish ectopic arrhythmias in such circumstances It may be mentioned that stimulation of the tuber nuclei of the hypothalamus, which are known to be concerned with the function of the para-sympathetic, produced slowing of the heart and lengthening of the A-V conduction time from 0 06 to 0 08 second (Beattie, 1932, a, b), but no ectopic arrhythmias were observed

That the importance of the sympathetic nervous system as efferent paths in ectopic arrhythmias of central nervous origin is not confined to those of hypothalamic origin is shown by the part it plays in the extrasystolic irregularities produced by the intracisternal injection of potassium phosphate, discussed above.

Also, *abnormal electro-encephalograms were reported during the occurrence of* " *neurogenic arrhythmias* " (Weinberg, 1947), and attacks of paroxysmal tachycardia were observed in infants with encephalitis (Bernuth and Steinen)

In electroshock ectopic arrhythmias were found in a considerable proportion of the electrocardiograms recorded in 304 major convulsions in 126 consecutive curarized patients (atrial 26 per cent , ventricular 18·7 and nodal 5 9), their incidence was much higher in seventy tracings taken from patients with cardiovascular disease, the corresponding figures being 47.1, 40 0 and 7·1 per cent respectively (Hejtmancik *et al*) In a series of ten patients treated with electroshock, eight showed arrhythmias of which auricular extrasystoles were the most frequent (Altschule *et al*)

In exceptional circumstances, however, stimulation of the vagus may produce extrasystoles in the experimental animal (*see* p 255). Regarding a possible central vagal origin of extrasystoles in man a clinical observation of Korth may be quoted in a digitalized patient of fifty-eight, with auricular fibrillation and an old-standing mitral lesion, numerous ventricular extrasystoles occurred after an apoplectic fit due to embolism in the basilar artery and resulting in a softening of the left cerebellar hemisphere The extrasystoles, which were abolished by atropine, were considered central in origin and due to an involvement of the vagal nucleus If the explanation is correct the observation would demonstrate in man a central vagal origin of extrasystoles in the presence of digitalis as a sensitizing agent This would be analogous to the experimental production of extrasystolic arrhythmias by peripheral vagal stimulation in dogs sensitized with aconitine, or to the extrasystoles elicited by stimulation of the central end of the vagus in chloroformed cats (Korth) The alternative explanation that the extrasystoles were due to impairment of vagal action by the cerebral lesion is unlikely in view of their abolition by atropine

The question of a central nervous origin of extrasystoles may be of medico-legal importance, as shown by the first of two cases reported by Lucke A man of fifty-four sustained concussion by a fall from a ladder, and a cardiac arrhythmia discovered after the accident was at first thought to indicate previous heart disease which was considered to have caused the accident Subsequent fuller investigations failed to reveal any evidence of a cardiac lesion prior to the accident and it was concluded that the accident was *the cause of the* arrhythmia This consisted in blocked auricular extrasystoles, the disturbance of conduction being abolished by 1 mg of atropine The arrhythmia was still present one year after the accident, though its character had somewhat changed (Lucke) In our opinion, unless there is proof to the contrary, in a case of this kind an arrhythmia may well have been present unnoticed for quite a time before the accident and may have caused the fall

Regarding the part played by the central nervous system in the production of ectopic

the impulses precipitating the arrhythmias travel also vary widely Regarding the efferent paths the predominant importance of the sympathetic became manifest at almost every stage of the discussion, but a few conditions have been shown to exist in which surprisingly the vagus enhances or precipitates ectopic impulse formation and the rôles usually played by vagus and sympathetic seem reversed

The relationship between extrasystoles and emotional factors is discussed in the chapter dealing with predominantly clinical aspects of such arrhythmias (*see* p. 448).

SUMMARY

In this chapter the influence of the nervous system in eliciting or modifying ectopic arrhythmias is discussed Using the term " nervous system " to include the action of autonomic nerves, reflexes, the central nervous system and psychological factors, this influence is profound and of great physiological and clinical importance

It is pointed out that in most cases, in which nervous influence precipitated or modified ectopic and allied arrhythmias, complex conditions were present which resulted in the heart's being predisposed to the exhibition of such disturbances of rhythm.

The influence of the nervous system in this respect is discussed in some detail under the following headings

Ectopic beats precipitated by direct (faradic) stimulation of vagus and sympathetic;
- due to reflexes
  - from the carotid sinus, including the part played by the presso-receptor nerves;
  - from the respiratory tract,
  - from the gastro-intestinal tract,
- precipitated from the central nervous system

The relevant literature about these aspects is reviewed and several personal observations are described

Regarding the relationship between emotional factors and ectopic arrhythmias the reader is referred to the appropriate section of the chapter on " Some mainly Clinical Aspects " of such arrhythmias (p 448)

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CHAPTER VIII

EXTRASYSTOLES, DRUGS AND ELECTROLYTES

INTRODUCTORY REMARKS

There is hardly a chemical compound which is not known to have precipitated extrasystoles in certain circumstances. It would be as unprofitable as it is impossible to give a complete list of such substances and to attempt anything like a review of the literature on this topic Instead, an endeavour has been made to select, in this chapter, certain compounds which are of a special physiological or clinical interest regarding their relation to extrasystoles, or ectopic arrhythmias generally, and to confine discussion to the more important aspects. Moreover, it is hoped that the various bibliographies will be found helpful by those who are especially interested in any particular aspect

As combination of drugs has often to be discussed some repetition is not entirely avoidable, but by making use of cross-references we have tried to reduce it as much as possible. Much work is in progress at the moment on some of the drugs discussed, for example on procaine and related compounds, so that many of the most recent papers could not be included and any conclusions on such compounds should be considered as necessarily provisional

DIGITALIS

Of all the innumerable drugs which have some relation to ectopic arrhythmias, digitalis unquestionably occupies pride of place It shows *par excellence* the dual property of being able to elicit, as well as to suppress, such disturbances of rhythm With a drug employed on such a vast scale, its modes of action are bound to assume the greatest importance, physiological as well as clinical

Experimental

Introductory Remarks

While a review of the complex mode of action of digitalis would be out of place in this book, a few remarks are opportune about its effect on the refractory phase and on cardiac excitability, these aspects having a close bearing on the subject under discussion

In this connexion it should be recalled that, in addition to its direct effect on cardiac muscle, digitalis exerts an indirect one through increasing vagal tone In the mammalian heart the latter is confined to auricles and the A-V node, since direct vagal influence does not extend to the ventricles

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(Lewis, Drury, Wedd, and Iliescu) In view of the method employed in such experiments (discussed in the section on quinine) such results were subsequently queried by Lewis and collaborators themselves, re-investigation of this problem with an improved technique revealed that digitalis invariably shortened the absolute refractory period in the ventricle of the tortoise (Love) and of the dog (Lewis and Drury) These conclusions were in accordance with those of Junkmann and subsequently were repeatedly confirmed (Schellong,

McLeod; Wedd, Blair and Dwyer) The pronounced shortening of the Q-T intervals n electrocardiograms of man during digitalis treatment also indicates a shortening of refractory period (Berliner) Certain reservations seem, however, to be necessary L and Drury, when reversing their original views, pointed out that what they termed the e tive refractory period (that is the interval required for a subsequent stimulus to yie *propagated* wave of excitation) is lengthened by strophanthin, and Schellong arrive similar conclusions

That digitalis diminishes the excitability of the heart has been known for a long t (Traube 1871, Tschistowitsch, Brandenburg, Hering 1907, Sollmann *et al*, Guthrie) seems desirable to recall such observations, as the contrary statement can be found in s textbooks, namely that digitalis increases cardiac excitability. Such statements are base the assumption, erroneous in our opinion, that the precipitation by digitalis of ectopic b indicates increased excitability of the heart. Such reasoning seems to us open to doubt s increased excitability alone does not give rise to ectopic impulses.

Experimental Investigations on Ectopic Arrhythmias Caused by Digitalis and Strophan

Amongst the earliest observers of arrhythmias caused experimentally by digitalis, Tra (1850–51) may be mentioned and particularly Boehm, who reported in 1872 that, in fr the "diastolic part of the wave was interrupted half-way by the rudiment of a second systo (our translation), and found similar conditions in dogs His explanation—that digit increases the contractility to such an extent that two contractions became necessary to exha it—seems a little naive to-day, though eighty years' intensive research have still not hausted the problem Other early reports include those of Popper (1889), François-Fra (1894) and Cushny (1897)

The first systematically to investigate electrocardiographically the arrhythmias occurr in dogs as a result of strophanthin and digitalis were Rothberger and Winterberg in 19 In all stages of strophanthin intoxication ectopic beats were found, originating, as a ru in the left ventricle During the early stages of the drug effect such ectopic beats occurr only if the normal impulse formation in the S-A node was inhibited by faradic stimulati of the vagus During higher degrees of intoxication they were observed without va stimulation, and with still more pronounced poisoning ventricular ectopic rhythms co pletely replaced sinus rhythm These results were confirmed by Egmond and by Sch (1927b)

The dose of strophanthin or digitalis necessary to elicit such ectopic arrhythmias vari as reported by different investigators In an early study on dogs Halsey found 19–33 p cent of the m l d of strophanthin necessary for precipitating terminal ectopic arrhythmi (precursors of ventricular fibrillation), whereas at least 40 per cent. were required if digita was employed Later investigations gave almost the same figure regarding strophanth (18 per cent , Hoekstra and Schleusing); whereas those for digitalis varied between 20–30 p cent in dogs (Seevers and Meek), and 50 per cent. (Levine and Cunningham) and 63 per ce in cats (Bauer and Reindell) If ephedrine was given in conjunction with digitalis, su arrhythmias were more pronounced and persistent, and ventricular fibrillation occurred an early stage (Johnson and Gilbert, Seevers and Meek).

One important feature of such ectopic arrhythmias, caused by digitalis or strophanthi

Egmond). As distinct from extrasystoles in the strict sense of the term, such experiment

digitalis or strophanthin arrhythmias have to be considered as due to increased automaticity of ventricular centres The importance of this distinction is discussed in the chapter on " Mechanism ".

In view of the paramount clinical importance of bigeminal rhythms due to extrasystoles attempts were made experimentally to produce this type of arrhythmia by modifications in technique.

[illegible]

and Scherf) The only method, known to us, by which it was possible to produce, by the systemic administration of strophanthin, extrasystolic arrhythmias with extrasystoles of constant shape and accurate coupling, is by its combination with the inhalation of a mixture of 25 per cent CO_2 and 75 per cent. O_2 (Goldenberg and Rothberger). Administration of such mixture at the stage of ectopic (pre-fibrillary) tachycardia quickly converted it into a polygeminal rhythm and finally into a true bigeminy This procedure was reversible, the former irregular tachycardia recurring within a few seconds on substituting air for the above gas mixture.

Another method consists in the *topical* application of digitalis to the surface of the exposed heart. As early as 1894 Langendorff observed abnormal arrhythmic pulsations after the application of digitalis or helleborein to the isolated apex of the frog's heart A similar method was used when strophanthin, lanatoside-C or digitoxin was applied in dogs to the exposed heart *in situ* (Scherf 1944, Kisch 1944) Figs. 161 and 162 illustrate arrhythmias produced in this way

Fig 161a shows persistent trigeminy recorded six minutes after the subepicardial injection of 0 05 cc. of a 0·1 per cent solution of ouabaine into the conus of the right ventricle. The first extrasystole of each trigeminus is accurately coupled to the preceding sinus beat and the interval between the two extrasystoles equals the coupling All extrasystoles have the same shape. The arrhythmia persisted for six minutes

Fig 161b demonstrates ventricular extrasystoles with accurate coupling and constant shape, occurring after every second sinus beat, the arrhythmia was elicited by brushing a 0 1 per cent solution of digitoxin on a circumscribed area of the conus of the right ventricle. Similar results were obtained by the application, to the epicardial surface, of a few crystals of strophanthin or digitoxin

The assumption that such extrasystoles originate in the area to which the drug had been [illegible] irregular ventricular tachycardia which had been elicited by the application of strophanthin (strophosid, Sandoz) to the conus area of the right ventricle During warming of this area a conspicuous increase in rate occurred, though the shape of the ectopic beats remained unchanged in the record

Extrasystoles produced in this way immediately disappeared when the sinus rhythm was inhibited by vagal stimulation This demonstrates that they were precipitated by the preceding (sinus) beat and were not due to an independent automatic activity of the ectopic centre

A more detailed analysis of the extrasystolic arrhythmias produced by such methods revealed several points of interest They occurred after a considerable latent interval, amounting, in the case of strophanthin, to about six, and in that of digitalis to about eleven minutes A similar latent period was seen with the topical application of barium, but not with that of sodium (Piccione and Scherf, *see* respective sections) Such arrhythmias lasted for a considerable time, that is up to twenty-two minutes in the case of strophanthin

FIG 161.—From experiments on dogs *a* Lead 2 Persistent trigeminy after the subepicardial injection of 0 05 cc of a 0 1 per cent solution of ouabaine into the conus of the right ventricle *b* Ventricular extrasystoles *with accurate coupling and* constant shape after every second sinus beat after *topical application of a 0 1 per cent solution of digitoxin to the conus of the right ventricle*

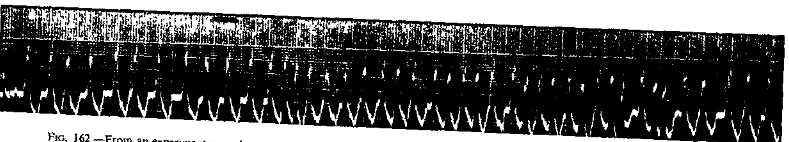


FIG. 162.—From an experiment on a dog The beginning of the tracing shows an irregular ventricular tachycardia elicited by the topical application of strophanthin to the conus area of the right ventricle Warming of this area (between the two marks on the record) resulted in an increase in rate of the ectopic rhythm.

and up to forty-five minutes in that of digitalis Extrasystoles could be elicited from any part of the auricles or ventricles which was tested by this method. If, as was occasionally observed, ventricular tachycardias occurred, they showed the same kind of irregular sequence as those precipitated by the focal application of barium or by the systemic administration of digitalis or strophanthin in larger doses

These observations emphasize an essential similarity between the arrhythmias caused by the topical application of strophanthin (or digitalis) and barium, as distinct from sodium, and warrant the conclusion that they are a specific drug effect and not due to local mechanical or osmotic stimulation. Furthermore, such extrasystoles have to be assumed to originate in one circumscribed focus in which they are precipitated by the preceding beat; they occur without the automatic impulse formation in other ventricular centres being altered Hence also, as distinct from the arrhythmias due to systemic administration of strophanthin or digitalis, the constant shape and accurate coupling of the ectopic beats (and the possibility of eliciting them from auricular centres) The significance of these views in relation to our conception of the mechanism of extrasystolic impulse formation, and also to its separation from automatic impulse formation, is discussed in the chapter on " Mechanism ".

In studies on isolated strands of Purkinje tissue of dogs' hearts digitalis or strophanthin caused arrhythmias akin to bigeminal or trigeminal contractions (Wachstein; Spuehler and Zwillinger; Ferranini).

Auricular ectopic arrhythmias caused by systemic administration of digitalis were reported by Cushny (1897)

Arrhythmias caused by injection of strophanthin into the fourth ventricle are discussed in the chapter on " Nervous System " (p 268)

Clinical Observations

The occurrence of arrhythmias in the course of digitalis treatment has been known for a long time. Mention must be made in this context of Traube's description of the irregular pulse (1850–51); similar observations were made by Lorain in 1870 and by Riegel in 1877 (*see* also Josué and Godlewski 1912, and chapters on " Historical Remarks " and on " Coupling ") In particular, the bigeminal pulse was bound to attract attention at an early stage.

It was soon recognized that different patients varied widely regarding the dose of digitalis necessary to produce irregular pulse and heart action.

Predisposing Factors of Ectopic Digitalis Arrhythmias

It is a curious fact that in normal subjects digitalis does not cause ectopic arrhythmias. This was recognized by Huchard as long ago as 1892, and later observations have shown that even lethal doses, taken accidentally or with the intention to commit suicide, do *not* precipitate extrasystoles, though abnormal rhythms and A-V block were found (Eckstein, Froment *et al*, Tomaszeski and Lapa, McGuire and Richards, Duvoir *et al.*, Albeux-Fernet and Welti, Bickel *et al*), unless structural heart disease is present (Wilkinson) While the statements that extrasystoles occur only in patients with hypertrophy or dilatation of the heart (Edens) or with increased serum calcium (Edens and Huber) were not confirmed, there is a great deal of evidence that ectopic digitalis arrhythmias are observed only in patients with some structural heart disease. This is already implicit in Huchard's writings of 1892 (*cp also* Fauconnet, 1904) Mackenzie (1905) emphasized the frequency with which digitalis causes bigeminal rhythm in patients with rheumatic valvular disease and with auricular fibrillation The opinion, expressed repeatedly (Huchard, Gallavardin, 1926a) that digitalis extrasystoles are especially common in patients with enlarged hearts due to

rheumatic mitral valvular disease, and that they carried an unfavourable prognosis (Huchard; Leconte, Edens and Huber; Gallavardin, 1926a) was confirmed by Scherf (1932) who found that, amongst twenty-one consecutive patients with digitalis bigeminy, twelve had mitral lesions and that sixteen of this series died within eighteen months after the arrhythmia had been discovered These figures are comparable with those of Edens and Huber who reported a mortality of 80 per cent. within two years While such extrasystoles *are very common in auricular fibrillation, they are by no means rare in sinus rhythm* We agree with Leconte's description that digitalis extrasystoles are a " geste de souffrance ", rather than with minimizing the prognostic significance of this kind of arrhythmia (Gold and Otto)

If structural heart disease is a predisposing factor for digitalis extrasystoles, it is not the only one This follows from the great individual differences regarding the dose required to produce them. While some patients with unquestionably diseased hearts can take large doses of digitalis over long periods without exhibiting any extrasystoles, though pronounced disturbances of conduction testify to the marked drug effect, others develop bigeminal heart action after very small doses. For example, in one observation, 0 1 gramme of powdered

ized patient soon after a mercurial diuretic had been given; this is due to a re-digitalization of the patient by re-absorption and re-circulation in the body of fluids with a high content of digitalis The other extreme is represented by patients who develop extrasystoles only after several years' treatment with large doses of digitalis In one patient, observed for many years, a woman with hypertension, grossly enlarged heart and auricular fibrillation, a weekly maintenance dose of 5·5 mgm of digoxin was taken for years with hardly any extrasystoles on periodical electrocardiographic examinations (Schott, unpublished observation)

The rate, at which the premature beats disappear after discontinuation of the drug, equally varies within very wide limits, ranging from a very few days to one month; it is known that it may take that time for the drug to be eliminated from heart muscle.

What the cardiac condition is which predisposes the heart to such arrhythmias, the nature of this " terrain cardiaque special " (Gallavardin, 1926a), is not known

Descriptive Features of Digitalis Extrasystoles

Extrasystoles caused by digitalis have two important characteristics with rare exceptions they are ventricular in origin, and their shape in the electrocardiogram is not constant whereas their coupling, practically, is.

Auricular Ectopic Digitalis Arrhythmias. It should be emphasized that the great majority of digitalis extrasystoles originate in the ventricles. While the cause of this is not known, it is likely that vagal tone, which is increased by the drug and which, in the mammalian heart, does not affect the ventricles, is of importance in this connexion The statement that such

vation may be added:

Fig. 163 reproduces records from an eighty-six-year-old woman with arteriosclerosis and moderate dilatation of the heart; blood pressure 180/90. Digitalis was prescribed by her medical adviser because of moderate dyspnoea, 0·8 mgm of digitaline Nativelle being

given as an initial dose, followed by a daily maintenance dose of 0·4 mgm. On the fifth day of this treatment the patient exhibited profound general muscular weakness, nausea and yellow vision, an electrocardiogram taken at that time is shown in Fig 163a It demonstrates auricular tachycardia with an auricular rate of 186, inverted P waves in leads 1 and



FIG 163*a*
Auricular tachycardia and multiform ventricular extrasystoles due to digitalis

2, and multiform ventricular extrasystoles The RS-T segments and T waves show a marked digitalis effect. The drug was discontinued immediately and ten days later another electrocardiogram (Fig 163b) showed sinus rhythm without extrasystoles, in the final deflections some digitalis effect is still present, though far less pronounced

Ventricular Ectopic Digitalis Arrhythmias. Whereas some authors are of the opinion that digitalis extrasystoles are constant in shape and thus do not differ from the common variety occurring spontaneously (for example, Lewis), we believe that, generally, their shape

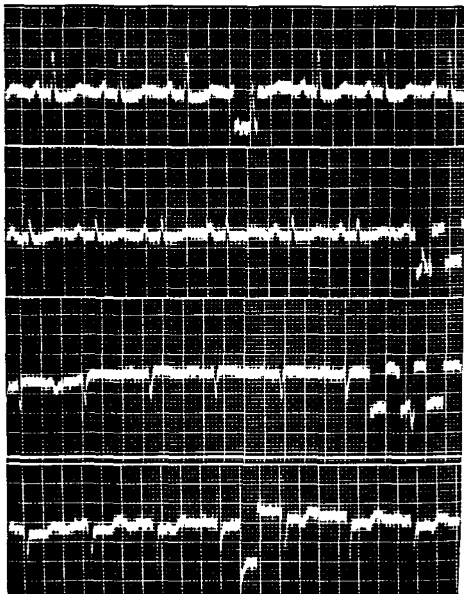


FIG 163*b*

From the same patient as Fig 163*a* Ten days after discontinuing digitalis Sinus rhythm For further explanation, see text

varies in the electrocardiogram, a view held also by others (for example Gallavardin, 1926a, Mahaim). In a series of fifty-eight consecutive cases with extrasystoles due to digitalis, such changes in shape of the extrasystoles were encountered in every case (Scherf 1931, 1932).

Often the form alters from extrasystole to extrasystole It is true that, in some cases, longer tracings have to be taken in order to detect greater variations in shape, and short records may reveal only differences in the height or depth of the several waves; in such instances differences in the appearances of the extrasystoles tend to become more pronounced as digitalis treatment continues (Scherf, 1927a). In other cases, however, conspicu-

been called multifocal, but such designation seems to us of questionable accuracy since disturbances of conduction of the extrasystoles originating in one focus cannot be excluded as the underlying mechanism and, actually, seems the more likely alternative in some instances. This view is supported by the observation that, in spite of their varying in shape, digitalis extrasystoles have a fairly constant coupling: in eleven out of fifteen cases variations in coupling did not exceed 0 02 second (*see also* chapter on "Coupling"). "Multiform" seems to be a better term

by this drug

If, at this stage, the exhibition of the drug is continued, further developments take place along one of three lines

(1) Bigeminy persists, (2) the extrasystoles disappear; (3) the extrasystoles increase in number and, with further continuation of digitalis treatment, ventricular tachycardia and, lastly, ventricular fibrillation ensue Each of these possibilities warrants a more detailed discussion

(1) Persistence of bigeminy, in the course of continuation of digitalis treatment in full doses, is comparatively rare. In such cases the number of extrasystoles does not increase

(2) In *other instances*, amounting to about 30 *per cent*, the *extrasystoles* disappear

(3) The largest, and clinically the most important, group reacts to the continued administration of digitalis by an increase in the number of extrasystoles The bigeminy changes into tri- or polygeminy, and eventually in ventricular tachycardia and ventricular fibrillation Several electrocardiographic aspects merit special consideration

One variety seen in more advanced digitalis intoxication is the occurrence of automatic idioventricular beats to which extrasystoles may be "coupled" in a similar way as



Fig. 164.—From a patient with auricular fibrillation. Automatic idioventricular beats and extrasystoles due to digitalis For further explanation, see text

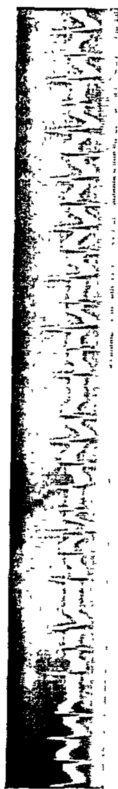


Fig 165.—Lead I. Polygeminy and ventricular tachycardia with alternating shape of complexes due to digitalis For further explanation, see text.

extrasystoles follow an automatic idioventricular beat with the same coupling as those coupled to supraventricular beats Such idioventricular beats should not be confused with extrasystoles They are recognized as such by their occurrence late in diastole. They also may show continual variations in form (Christian, 1915b)

Sometimes automatic and extrasystolic beats have the same form in the record, which indicates origin in the same focus (compare the great similarity between the second extrasystole and the second automatic beat [the thirteenth complex] in Fig 164), similar observations have been made by Rachmilewitz and Scherf, and by Scherf and Schott (*see also* chapters on " Pararrhythmia ", and on " Mechanism ")

Other varieties are polygeminy and ventricular tachycardias with alternating shape of the ectopic beats Fig 165 illustrates both The tracing was obtained from a patient with emphysema, shortly after the injection of 0 2 mgm of strophanthin It shows auricular fibrillation. The first supraventricular beat is followed by two, the second by seven ventricular extrasystoles, all having different shapes The third conducted beat is followed by a ventricular tachycardia with alternating shape of the complexes In some cases such alternation is maintained for considerable periods In order to explain the alternation various views were put forward

(a) A rather complicated circus movement was assumed, involving the two ventricles alternately (Gallavardin, 1926a, Palmer and White) As there are no data pointing to the existence of such paths in the ventricles, this hypothesis, for which no proof was attempted, can be disregarded

(b) The presence of two centres of impulse formation alternating in action was postulated by Felberbaum It has to be remembered, however, that not infrequently such tachycardias are entirely regular and that no alternation of cycle length is associated with alternation of form It would be difficult to imagine an exactly equal rate of impulse formation in two centres situated in different ventricles This hypothesis has to be considered improbable, though not impossible

(c) The most probable explanation seems to be the assumption of impulse formation in one centre with alternation of intraventricular conduction (Scherf and Kisch) This view is supported by experimental and clinical observations regarding similar alternation of ventricular complexes in instances of auricular tachycardia, in which such alternating intraventricular conduction is observed in respect of supra-ventricular beats An example is provided in Fig 137 in the chapter on " Coupling "

Such tachycardias are often precursors of ventricular fibrillation and therefore have an ominous significance (" tachycardie terminale ", Gallavardin, 1926b) In elderly patients they may be observed after moderate doses of digitalis (Currens *et al*) They call for immediate discontinuation of the drug Occasionally this arrhythmia is encountered without digitalis (four out of eighteen cases, Scherf and Kisch, *see also* Fig 198) In one such case the tachycardia was observed, in an otherwise healthy subject, for many years and could always be stopped by digitalis (Scherf and Kisch) Ventricular tachycardia, even with

time when rapid digitalization (for example, Eggleston's method of administering within twenty-four hours large doses of the drug calculated by the patient's weight) was practised on a wider scale (Schwensen, Felberbaum, Reid 1923, 1924, Marvin, Palmer and White) Owing to the present revival, in the U S A , of this way of digitalis administration such arrhythmias are being described again with increasing frequency (Levine, Stone; Fremont and King)

While ventricular tachycardia, and particularly its variety with alternating complexes,

if caused by digitalis, is an absolute contra-indication against continuing medication, conditions are more complicated if bigeminal rhythm or single extrasystoles occur during digitalis treatment According to Mackenzie digitalis bigeminy " is a signal to lessen at once " the dose, " no good is obtained by pushing it further ". Christian (1915b) stated that " it is a sign of omission of digitalis " Leconte's view was that it is permissible to continue the treatment if single extrasystoles occur, but that it is necessary to stop the drug immediately the number of extrasystoles increases.

Our views may be summed up thus: If extrasystoles had not been present before the exhibition of digitalis and occur in the course of its employment, great care on the physician's part *is always called for; to continue with the drug always requires special precautions* and, if at all practicable, repeated electrocardiograms. Furthermore, each case must be considered individually and we would discourage all generalizations. With these provisos we recommend that, having regard to the arrhythmia, the drug be discontinued if the maximum beneficial effect on congestive heart failure had been attained which can be expected in the *individual case, in other words, if compensation had been restored as fully as is reasonable* to expect In nearly all such cases a smaller maintenance dose has to be re-instituted, which can usually be effected after a short interval of, say, 2–3 days The situation is different in cases in which extrasystoles occur at a stage of treatment when congestive heart failure is still pronounced and when, with further exhibition of the drug, further improvement can be expected In such cases continuation of the drug in temporarily reduced doses under strict supervision and repeated electrocardiographic control is justified. This view is based on the fact, discussed above, that, for the development of such arrhythmias in the course of digitalis treatment, the condition of the heart in the individual case is of as much importance as the dose of the drug, and that in a certain proportion continuation of medication does not increase the number of the premature beats Should the arrhythmia become more pronounced, immediate cessation of the drug treatment is imperative.

Similar problems sometimes arise in the treatment of certain arrhythmias In one such instance, a patient with Lutembacher's syndrome and auricular flutter, with occasional ventricular extrasystoles, bigeminal heart action developed in the course of digoxin treatment, the cautious continuation of drug treatment made the desired conversion into auricular fibrillation possible (Schott)

It will have become evident that success or failure will, in many cases, depend on the optimum adjustment of the dose of the drug in the individual case and much has to be left to the physician's discretion and experience This is not possible with the administration of large amounts of the drug within a short time (*see* above) For the same reason we advise to employ the same principle when using intravenous injections of strophanthin we recommend that the first dose should not exceed 0 15 mgm and the patient be closely observed, for the occurrence of premature beats, for thirty minutes. Only in the absence of extrasystoles should the daily dose be increased to 0 25 mgm and the strict supervision of the patient should be continued after each injection. 0 5 mgm. should never be exceeded and this dose seems rarely necessary. Strophanthin should not be given if the patient had taken digitalis within ten days before the intended injection With these precautions the use of strophanthin can be considered safe (Laubry and Leconte, Simici)

The Abolition of Extrasystoles by Digitalis

Extrasystoles which are not due to digitalis usually disappear when this drug is given This therapeutic effect upon extrasystoles of digitalis is discussed in the section on " Treat- [illegible] In one investigation [illegible] out [illegible] ular [illegible] extrasystoles shortly before death (Otto and Gold).

Other Glucosides with Digitalis-like Action

Regarding extrasystolic arrhythmias, too, such glucosides have an action similar to digitalis. Experimentally, bigeminal action was observed after the administration of apocynum cannabium (Hecht) and squills (Turnbull). The effect of scillaren upon isolated strands of *Purkinje tissue was similar to that of digitalis or strophanthin, described above* (Rothberger and Zwillinger). The administration of water-insoluble glucosides of squills caused extrasystoles in twelve out of twenty-five cases (Maher and Sittler). Similar effects were seen with foliandrin (Schindel and Braun), and with helleborein, both experimentally (Hering, 1901) and in clinical observations (Scherf, 1937). In all such instances the ectopic beats were ventricular in origin and showed continual variations in shape.

SUMMARY

Experimental Investigations

Some work on the effect of digitalis on the refractory period and on the excitability of the heart is briefly discussed. Systemic administration of strophanthin or digitalis results in ectopic arrhythmias, originating in a ventricle, whereby the ectopic beats have varying shape and varying coupling in the electrocardiogram. Extrasystoles in the strict sense of the term (that is with accurate coupling and often of constant shape), so common in clinical practice, cannot experimentally be produced by the systemic administration of these drugs, except by the concomitant inhalation of a mixture containing 25 per cent CO_2 and 75 per cent O_2. True extrasystolic arrhythmias can, on the other hand, be elicited by the topical application of these drugs to the surface of the exposed heart *in situ*. Such arrhythmias are discussed in some detail and the importance of such investigations for the experimental reproduction of a common clinical disturbance of rhythm is emphasized. The significance of such investigations is pointed out regarding our views about extrasystolic, as distinct from automatic, impulse formation, and about the mechanism of the origin of extrasystoles, discussed in more detail in the appropriate chapter.

Clinical Observations

It is pointed out that digitalis or strophanthin does not cause extrasystoles in normal subjects and that some predisposing factors are necessary for such arrhythmias to be precipitated by these drugs. Structural heart disease is one such factor, some aspects of which are discussed in detail. The dose of the drug necessary to elicit extrasystoles varies widely in different cases, and so does the time required for them to disappear after cessation of medication. Of the features of digitalis extrasystoles, the comparative rarity of auricular ones is stressed and one personal observation of such an instance is described. The varying shape but fairly constant coupling of ventricular digitalis extrasystoles are emphasized as important characteristics. The development of extrasystolic arrhythmias during digitalis treatment is discussed under the three headings: (1) persistence of bigeminy, (2) disappearance of extrasystoles during continued digitalis treatment, (3) increase in the number of extrasystoles, resulting in tri- or polygeminy, ventricular tachycardia and ventricular fibrillation. The occurrence of automatic idioventricular beats is mentioned as one variety of such arrhythmias. The association of automatic idioventricular beats with extrasystoles is discussed and illustrated by a personal observation. Ventricular tachycardias with alternation of the complexes are described in some detail, illustrated by one personal observation, and the various explanations of this arrhythmia are critically discussed. The dangers, as exemplified by such arrhythmias, of the administration within a short time of

in the employment of strophanthin, given intravenously, is briefly discussed. Some work on the effect of other glucosides with a digitalis-like action is briefly reviewed.

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QUININE AND QUINIDINE

Some Introductory and Historical Remarks

Though Senac wrote in 1749.

" [illegible] constante & [illegible]

the value of quinine was not generally known until it was rediscovered by a patient of Wenckebach (1914) who realized the great importance of this observation; Wenckebach retold the story in 1923. It is true that, long before 1914, individual observers, amongst them eminent clinicians, recommended quinine, often with other measures, for the treatment of patients with irregular heart action, some of whom may well have had extrasystolic arrhythmias (Oppolzer 1866, Sir Walter Foster 1890, Hochhaus 1907, Huchard 1908), and it must have been as early as 1892 that Wm Pepper (of the University of Pennsylvania) recommended cinchona and bromides to Walsh who suffered from extrasystoles for decades (Walsh, 1927)

In 1918 quinidine, another alkaloid of the cinchona bark and an isomer of quinine, was

found by Frey to be more effective than quinine in the treatment of cardiac arrhythmias and is now universally used for this purpose The note about quinidine in the epitome of the U.S *Pharmacopea and National Formulary of* 1916 " at one time recommended as a cheap substitute for quinine. Inferior and obsolete " (White, Marvin and Burwell) thus became obsolete

Frey's observations about the superiority of quinidine over quinine were repeatedly confirmed (Lewis, Drury, Wedd and Iliescu; Drury, Horsfall and Munly; Clerc and Deschamps, Boyer) Lewis *et al.* (1922) found quinidine about five to ten times more effective than quinine According to Weisman (1942) commercial quinidine contains 80 per cent of pure quinidine, which is a marked cardio-vascular depressant, and 20 per cent of hydroquinidine which has only slight depressant properties

While, at present, quinidine sulphate is almost exclusively used in the treatment of cardiac arrhythmias it should be remembered that, in this respect, qualitatively quinine has the same effect as quinidine.

Experimental Findings

The quinine alkaloids are general cell and protoplasmatic poisons Their most important effects upon the heart can—somewhat artificially—be summarized thus

(1) *Effect on excitability*
(2) Effect on impulse formation
(3) Effect on refractory period
(4) Effect on vagus
(5) Effect on conductivity

While some particulars of the above modes of action, as far as they are relevant in the context of this book, will be briefly discussed under these headings, it should be emphasized that the various properties are interdependent and that it is thus hardly ever possible fully to analyse the resulting effect in a given set of circumstances

(1) Effect on Excitability

A depressant effect, upon excitability, of quinine alkaloids has been demonstrated in various ways (Hofmann 1915, Hirschfelder and Cervenka) The threshold for eliciting ectopic beats by electrical stimuli was found to be raised by quinine alkaloids (Hofmann 1915, Drury *et al*, Lewis *et al*, 1921, Wedd, Blair and Gosselin, Wégria and Nickerson). The chronaxie of the myocardium is increased (Espanés) In experiments on cats and dogs, treated with quinine, even prolonged faradic stimulation of the ventricles did not elicit persistent fibrillation (Hecht and Rothberger, Boekelman) In the perfused surviving heart of man quinine was found to diminish contractility, stimulus formation and excitability (Boden and Neukirch)

(2) Effect on Impulse Formation

Like so many compounds, cinchona alkaloids may suppress as well as precipitate ectopic beats The first of these predominates

Depression of ectopic impulse formation was observed by Santesson in 1893 in the [illegible]
et al., Clerc and Deschamps; Haskell, Friedberg and Levinson) Those produced by strophanthin responded in the same way Suppression of ectopic arrhythmias elicited in dogs by means of barium were stated by Singer and Winterberg to be abolished by quinine, but this

(3) Effect on Refractory Period

In considering the effect, upon the refractory period, of quinidine it has to be noted that its direct effect may be modified by its paralysing action on the vagus and by its effect on excitability

That quinidine lengthens the refractory period, as it had first been reported by Santesson in 1893, seemed established by repeated subsequent confirmations (Drury, Horsfall and Munly; Lewis, Drury, Iliescu and Wedd; de Boer; Junkmann and Starkenstein; Decherd and Ruskin) Such work was based on the determination of the time interval at which cardiac muscle responded to an early testing shock applied after a conditioning shock. It was then found that the response or non-response of the heart to a test shock, applied in such circumstances, was not a reliable criterion for determining the refractory period, as non-response may be due, not to absence of excitability, but to extinction of the impulse by disturbances of conduction If this source of error was eliminated, shortening, by quinidine, of the absolute refractory period was found in the ventricle of the tortoise (Love) and of the dog (Lewis and Drury). This does not, however, affect what Lewis and Drury termed the *effective* refractory period, namely, the interval required for a subsequent stimulus to yield a propagated wave of excitation: this effective refractory period is lengthened by quinidine. Experiments on isolated strands of Purkinje tissue did not yield uniform results (Berk and Wachstein).

(4) Effect on Vagus

There is general agreement that quinidine paralyses the vagus to a greater or less extent This vagal action increases the direct effect of quinidine upon the auricles as it tends to prolong the refractory period and to slow conduction. Differences of opinion exist as to the site of the drug effect, but a discussion of the various views is outside the scope of this book (*see* Dale, Clerc *et al.* 1922, Lewis *et al* 1922, Hiatt *et al*) Recently, a sympathicolytic effect of quinine and quinidine has also been described In dogs quinidine counteracts the pressor effect of epinephrine and of the stimulation of the splanchnic nerve (Hiatt, 1950)

(5) Effect on Conductivity

This may be summed up by quoting Lewis (1925, p 359) " In fact the general statement may be made that the alkaloid quinidine depressed conduction in all the muscular tissue of the heart . .".

Clinical Observations

As stated in the introductory remarks to this section, appreciation of the value of quinine in the treatment of extrasystoles is due to Wenckebach (1914), and of the superiority of quinidine, to Frey (1918) Their reports about the beneficial effects of these



Fig. 166.—From an experiment on a dog The beginning of the record shows bigeminal rhythm resulting from faradic vagal stimulation during the action of aconitine Quinidine transformed this arrhythmia into ventricular tachycardia, shown in the second part of the record From Scherf and Siedek, *Z ges exp Med.*

alkaloids were soon confirmed (Smith 1922; Deschamps; Levine and Fulton, Gouley and Soloff) Some dissenting opinions (for example, Lian and Blondel), while understandable in view of the occasional refractory case, can be disregarded

It was stated by Singer and Winterberg that quinidine suppresses ventricular extrasystoles more readily than auricular ones.

The detailed mode of action by which quinidine abolishes extrasystoles in man cannot be stated with any degree of certainty. The result is likely to be due to a combination of several factors, namely the effect of the quinine alkaloids on excitability, stimulus formation and perhaps also on conductivity and refractory period.

Experimental and Clinical Observations on Absorption and Elimination

In connexion with the practical application of these compounds, data concerning their rate of absorption and elimination are important, some relevant papers may be briefly discussed

Lewis *et al.* (1922) studied the effect of specially purified cinchona alkaloids in patients with auricular fibrillation After one single dose of 0·8 gramme of quinidine an effect was first noticeable after thirty minutes and was fully developed after one-and-a-half and three-and-a-half hours It had subsided after twenty-four to thirty hours, save in exceptional cases when some residual effect could still be traced after forty hours

The results obtained by Weisman (1940) in dogs are in agreement with the findings of Lewis and collaborators Weisman found that after a single *small* oral dose of 100 mgm. the maximum concentration in the heart muscle was reached in about thirty minutes and no trace was present at the end of four hours When repeated doses of 100 mgm. each were given three or four times at one-hourly intervals the maximum concentration in the myocardium was seen after two hours After a single *large* dose of 585 mgm the maximum concentration in the heart muscle was observed in about one hour and it took seven hours before the last trace had disappeared from the heart If approximately the same large dose of 585 mgm was given in three divided doses at one-hourly intervals (200 mgm three times) the maximum concentration in the heart was reached only after two hours and attained only 50 per cent of that produced by giving the same amount as a single dose. Similar results were obtained by others (Weiss and Hatcher) Comparable time relations were found in man by Sagall, Horn and Riseman who used the changes in the Q-T interval as criterion to measure speed and duration of the effect of this group of drugs.

This difference regarding the maximum concentration of quinidine in the heart and the speed at which it is reached is important for the mode of clinical application of this drug: it has often been observed that, for the purpose of stopping auricular fibrillation or paroxysmal tachycardia, the exhibition of quinidine in a few large doses is superior to that of the same total quantity in more frequent smaller single doses.

Linenthal *et al* (1947) found that, in man, after one single dose of 0·2–0 6 gramme of quinidine, the alkaloid could be traced in the plasma after fifteen minutes; maximum concentrations were found after one to three hours and maintained for two to three hours, appreciable amounts could still be traced after eight to twelve hours. According to Linenthal and Freedberg, following an oral dose of 0·2 gramme of quinidine the peak level of the drug in the plasma was 0 8 mgm per litre while it was 2·7 mgm. per litre when a single oral dose of 1 0 gramme had been given. There was always a clear correlation between plasma [illegible] plasma levels [illegible]

dose; the average residual level after twelve to eighteen hours was 42 per cent. of the peak level Such observations that this alkaloid can be traced in the blood many hours after the exhibition of one single dose conflict with the experimental results of Weisman, and of

Weiss and Hatcher, discussed above. They are of interest in view of the generally accepted view that the pharmacological effect is clinically limited to a few hours and that the drug is quickly eliminated Personal experience shows, however, that the effect of one oral dose lasts longer than some of the experimental work would lead one to expect.

A comparative study of the plasma levels reached with the same total daily dose of about 1 gramme by different members of this group of drugs showed considerable differences: the plasma concentrations of cinchonine were generally less than 5 per cent. of those of quinine, and those of quinidine (and cinchonidine) were intermediate between these two extremes (Taggart *et al.*)

Quinidine is partly destroyed in the liver (Plehn) and partly eliminated by the kidneys. According to Taggart *et al*, less than 5 per cent is excreted by the kidneys Renal excretion is relatively smaller with the exhibition of one large dose than with the administration of the same amount in divided doses. For this reason Wiechmann recommended to give the largest possible doses in as few fractions as possible

After *intravenous* administration these alkaloids disappear quickly. Weiss and Hatcher found in a cat that, after one single injection of 59 mgm of quinidine, 95 per cent. had disappeared from the blood within five minutes and after one hour only 1 per cent could still be traced. Similarly, seven minutes after one single injection of 10 grains of quinidine Weisman (1940) found only 6 per cent in the blood

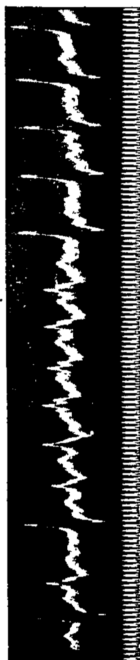
Ectopic Arrhythmias Caused in Man by Quinidine

In accordance with experimental investigations, clinical observations have shown that, sometimes, quinidine may precipitate ectopic beats, or increase the number of those previously present

The majority of such observations were made in cases of auricular fibrillation in which, in the course of quinidine treatment, beats with abnormal ventricular complexes were recorded (White, Marvin and Burwell; Lewis, Drury, Wedd and Iliescu; Levy; Maynard). Such beats occur, sometimes in groups of three or four in succession, at other times in greater numbers presenting as short periods of paroxysmal tachycardia. Lewis *et al.* found such abnormal complexes in 25–30 per cent of their observations, and since they were absent before, and subsided soon after the discontinuation of the alkaloid they were unquestionably caused by it. They tended to occur particularly at a time when quinidine had slowed the auricular rate, and showed constant shape in the electrocardiogram, but varying coupling. Differences of opinion existed, however, whether such beats actually were ectopic in origin: [illegible] White, [illegible] beats [illegible], who found the number of such beats increasing if quinidine was continued after the first appearance of isolated beats of this kind, thought they were supraventricular in origin, and attributed their aberrant intraventricular conduction to an increase in auricular rate due to vagal paralysis In one single case, on the other hand, Wilson and Wishart recorded such beats for two to three minutes after intravenous injection of quinidine and considered them to be extrasystoles

We have made similar observations in two cases of auricular fibrillation during quinidine treatment (Fig 167). The patient in whom Fig 167a was obtained developed the abnormal beats on the third day of treatment after a total dose of 2 grammes (after a test dose of [illegible]

ventricular complexes, which is suggestive, but by no means conclusive, of a ventricular



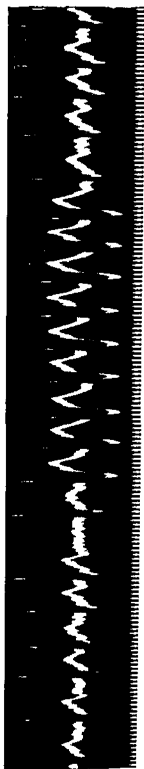


Fig 167.—Arrhythmias observed during quinidine treatment From two different patients For explanation, see text.

ectopic origin of the abnormal beats While in such cases it is not possible to decide with any degree of certainty whether such beats are ventricular ectopic ones, or supraventricular in origin with aberrant intraventricular conduction, complexes which we have observed, after the intravenous injection of quinidine, in cases of paroxysmal auricular tachycardia can definitely be considered to be extrasystoles, as a confusion with aberrantly conducted sinus beats is hardly possible

Several clinical instances have been reported in which short paroxysms of ventricular tachycardia and even ventricular fibrillation were observed following the oral (Davis and Sprague, Kerr and Bender) or intravenous (Schwartz and Jezer, Jezer and Schwartz) administration of quinidine. In most of these cases complete A-V block was usually also present; its relation to the abnormal response to quinidine is obscure In two cases short *paroxysms of ventricular fibrillation were invariably observed on several occasions after* each intravenous injection of quinidine, so that a coincidence can be excluded In the case of Diamondstone *et al* the paroxysmal ventricular tachycardia cannot with certainty be attributed to the large dose of quinine which had been taken (and which also had caused amaurosis), since the patient may have had a concurrent myocardial infarction

For particulars about the therapeutic use of quinidine, *see* section on " Treatment "

SUMMARY

Experimental Findings The various effects, upon the heart, of quinine and quinidine, as far as they are relevant to the subject of this book, are briefly reviewed, namely, their effect on excitability, impulse formation, refractory period, vagus and conductivity. It is pointed out that, while a depressing effect, upon ectopic beats, of these alkaloids predominates, in common with many other compounds they may also have the reverse effect, that is, precipitating ectopic arrhythmias

Clinical Observations are in agreement with experimental findings The importance of the quick rate of absorption and elimination of quinidine for its mode of application in clinical medicine is emphasized; some relevant data are reviewed Two personal observations are described which demonstrate the precipitation, by quinidine, of beats with abnormal complexes, occurring in groups, the differential diagnosis of which is discussed. The literature on ectopic arrhythmias caused by quinidine is briefly reviewed

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ATABRINE

A certain number of compounds, though chemically unrelated to quinine, exert upon the heart a quinine-like action. They include papaverine, trasentin, some local anaesthetics and antihistaminics, syntropan, and atabrine (Dawes).

Atabrine, a synthetic anti-malarial drug of this kind, inhibits ectopic impulse formation in the heart. Other quinine-like actions include its antagonistic effect to epinephrine on blood pressure (Storm, Melville) It also abolished auricular fibrillation in the dog (Gertler and Karp). Toxic effects consist of anorexia, respiratory disturbances, yellow discoloration of the skin, pain in the epigastrium and also extrasystoles (Motta; Storm; Smith and Stoeckle) Different species seem to vary in their susceptibility to the drug

According to Shannon *et al* atabrine di-hydrochloride can in man be given intravenously in doses not exceeding 0 4 gramme without untoward effects provided it is injected slowly, but this is not recommended as a routine measure.

Clinically atabrine has been successfully employed in the treatment of auricular fibrillation and paroxysmal tachycardia (Ganguli; Gertler and Yohalem; Vega Diaz)

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S[illegible]

FAGARINE

Fagarine, an alkaloid obtained from the Argentinian plant *fagaro cocco*, has been known since 1932 to be a cardiac depressant (Stuckert and Sartori) Subsequently, Espanés established that it raises the fibrillation threshold for faradic stimulation and reduces the incidence of ventricular fibrillation after ligation of coronary arteries

The therapeutic possibilities of this drug attracted greater interest during the Second World War, when quinidine was scarce, and alpha-fagarine hydrochloride was recommended for the treatment of cases of auricular flutter and fibrillation (Deulofeu *et al*; Taquini) In one case, reported by Taquini (1945), multifocal ventricular extrasystoles were observed after the administration of the drug which can only be given intramuscularly. Subsequently, Scherf, Silver and Weinberg gave fagarine to thirteen patients with auricular flutter or fibrillation, or paroxysmal tachycardia; six of these developed multifocal ventricular extrasystoles and in two instances ventricular fibrillation ensued. Only two of the patients with multifocal extrasystoles had premature beats before the drug was administered.

In view of these observations fagarine has to be considered too dangerous to be employed in man

It should, however, be emphasized that, in the dog, even intravenous injection of relatively large doses does not precipitate extrasystoles while instantly abolishing auricular flutter and fibrillation, without causing either a fall in blood pressure or dilatation of the heart (Scherf, 1948) Such observations encourage the hope that some modification of fagarine may result in a drug which, though effective, is free from the above dangerous side-effects The recent investigations of DiPalma and Lambert, according to which the presence of a methoxy group is essential for the effect, upon arrhythmias, of quinidine, fagarine and other compounds, may point the way in which the search for such a remedy might be undertaken

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CHLOROFORM

While chloroform is now rarely used as an anaesthetic, the arrhythmias caused by this compound are of great historical—apart from the physiological and clinical—interest For it is due to the study of the chloroform arrhythmias that the importance of ectopic beats and ventricular fibrillation was first appreciated and the close relationship between these two arrhythmias realized

Experimental

be assumed to have been due to ectopic beats

The probl

collaboration

0 5 per cent

cardiac rhythm were observed and ectopic beats were rare Inhalation of chloroform in concentrations between 0·5 and 1 per cent, on the other hand, caused ectopic beats invariably, such arrhythmias usually disappeared if the concentration of the gas was further increased to above 1 5 per cent. and did so invariably with concentrations above 2 per cent

The injection of 0 065 mgm. of epinephrine during the inhalation of lower concentrations of chloroform caused ventricular fibrillation whereas, with higher concentrations of chloroform, the same dose of epinephrine precipitated only isolated ectopic beats Struggling of the animal or stimulation of the accelerans fibres had the same effect as epinephrine (Levy, 1912). It could be demonstrated that the arrhythmias resulting from the combination epinephrine-chloroform were not due to a rise in blood pressure and that they could be *abolished by severing the vagi (Levy, 1913), this effect of vagotomy was attributed to the* tachycardia with the resultant shortening of diastole (Nobel and Rothberger) Ventricular fibrillation caused by nicotine during light chloroform anaesthesia was shown not to be a vagal effect (Levy, 1926)

Levy became convinced that sudden death during chloroform anaesthesia was due to ventricular fibrillation From his extensive investigations he concluded that it is during *light* chloroform anaesthesia that the heart is in the condition of greatest irritability, during which any stimulation of the adreno-sympathetic system may cause death due to ventricular fibrillation (1913) During *deeper* anaesthesia with chloroform, on the other hand, cardiac function is only depressed, but no arrhythmias occur Such depression of function by chloroform was also found in isolated Purkinje fibres of the dog's heart (Ishihara and Pick)

Levy's findings were repeatedly confirmed (Cluzet and Tixier; Bardier and Stillmunkès, Tiemann, Beattie, Brow and Long, 1930, 1936; Trimble) Other investigators, however, obtained different results Such apparent contradictions are largely attributable to differences in the species of animals used, in the drugs employed for pre-medication, and in the dosage of chloroform (Embley, Caine and Reynolds; Meek, Liebenow and Orth) The difference in the reactions of different species becomes apparent from the observations of Embley who found ventricular fibrillation during inhalation of chloroform in three out of five experiments on cats, but was unable to reproduce in dogs the results which Levy had obtained in cats Fibrillation was never observed Smirnow, on the other hand, reported ventricular fibrillation, resulting from the combination chloroform-epinephrine, in dogs, but not in cats In a recent comprehensive review of the action of chloroform (Waters) only one instance of ventricular tachycardia was found in over three hundred inductions with chloroform on 120 dogs Deliberate maladministration (overdosage) caused marked depression of sinus node activity and abnormal automatic beats. Intravenous injection of epinephrine (0 01 mgm per kilo) during chloroform anaesthesia (eighty-two injections) produced ventricular tachycardia twenty-one times and ventricular fibrillation seven times. Pre-medication with atropine (0·5 mgm. per kilo) did not prevent epinephrine-chloroform tachycardia, but DHE-45 (0 4 mgm per kilo) afforded protection.

Frommel's investigations (1927, 1928) emphasize even more strikingly the importance of the species employed in such experiments: working on guinea pigs he found that ectopic beats occurring during chloroform anaesthesia were not influenced by the injection of epinephrine and he went as far as to recommend epinephrine as treatment for accidents occurring during chloroform anaesthesia This may be mentioned as a rather glaring example of an indiscriminate application to a clinical problem of results obtained in experimental work.

Quinine and quinidine prevent ectopic arrhythmias caused by chloroform, and by chloroform + epinephrine (Bardier and Stillmunkès, 1926) Similarly, decerebration of cats at the Sherrington level abolished ectopic beats produced by chloroform and, if performed prior to the administration of the anaesthetic, prevents such arrhythmias (Beattie, Brow and Long, 1930, 1936) This is discussed in some detail on pp 267–268. In dogs, antihistaminics (pyribenzamine, antistine) in relatively large doses inhibited ventricular fibrillation induced by chloroform and adrenaline, but such effect was inconstant and only of short duration (Levitan and Scott). Regarding the effect of atropine, *see* section on "Atropine".

Clinical Observations

Employing the electrocardiogram in a series of six patients Cluzet and Tixier found ectopic beats during chloroform anaesthesia in two instances. Hill investigated this problem electrocardiographically in seventeen cases, in sixteen of these special attention was paid to the induction period. In seven instances numerous ectopic beats were recorded, closely resembling the arrhythmias seen in experimental work. Sometimes they occurred only when the patient was struggling, an observation fully in accordance with those of Levy discussed above

Waters, in the monograph already referred to, tabulated the various arrhythmias recorded in fifty-two patients during chloroform anaesthesia (Table X on p 71). These included thirty-six instances of ventricular extrasystoles and twenty (!) of ventricular tachycardia, in only seven no irregularities were found These observations emphasize the risks inherent in this anaesthetic and seem to give little, if any, support to the contention, contained in that monograph, that " much undeserved blame was being placed on an agent which for almost a century has been used extensively and skilfully by practitioners "

SUMMARY

The extensive investigations of Levy demonstrated that in cats light chloroform anaes-

review of the literature reveals many conflicting reports and it could be shown that such discrepancies are largely due to differences in experimental technique. The different reaction of various species is of particular importance. It can be considered established that ectopic arrhythmias occur in man during chloroform anaesthesia and that in man, as well as in most species used in experimental work, fatal ventricular fibrillation can be precipitated during chloroform anaesthesia by the exhibition of epinephrine and allied compounds Struggling has an effect similar to that of epinephrine and great care has to be taken in this respect by the anaesthetist in the increasingly rare instances, in which chloroform is used as an anaesthetic

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CYCLOPROPANE

Cyclopropane is a cyclic hydrocarbon (trimethylene). It is now widely used as a general anaesthetic as it produces unconsciousness within one or two minutes and patients are awake within ten minutes of discontinuing the anaesthetic.

Experimental

When this compound was first investigated, prior to its introduction as an anaesthetic, arrhythmias resembling missed beats were observed in the blood pressure tracings (Lucas and Henderson) Such arrhythmias disappeared quickly when the concentration of the gas was reduced.

As cyclopropane was used more extensively as an anaesthetic it became recognized that, next to chloroform, this gas is most apt to produce ectopic arrhythmias At first ectopic ventricular beats occur singly and at long intervals, then more frequently, subsequently their number further increases, multifocal ectopic beats are observed and, finally, ventricular tachycardia and ventricular fibrillation may ensue.

... views have been expressed regarding the underlying mechanism At first it was

be anoxia, in the presence of which ectopic beats were said to be ... concentrations of cyclopropane, such arrhythmias were reported to resemble those seen in anoxia (Robbins and Baxter 1937, Robbins 1940) With adequate respiration and ample supply of oxygen, on the other hand, concentrations of cyclopropane of 30 per cent above those producing respiratory paralysis were stated not to cause ectopic arrhythmias.

This view that anoxia plays a decisive rôle in the production of cyclopropane arrhythmias was not confirmed (Lee *et al.*) and, if the effect of anoxia on the cardiac action generally ... Generalized anoxia, while producing marked disturbances ... not, as a rule, cause ectopic arrhythmias; on the con... ample, extrasystoles due to aconitine, are abolished

by anoxia (Scherf) It is only local anoxia, that is, ischaemia of circumscribed areas as in myocardial infarction or coronary stenosis, that it is apt to cause ectopic beats (*see* p 420)

Another view was that only light anaesthesia with cyclopropane causes ectopic irregularities whereas deeper anaesthesia abolishes them (Guedel), but the existence of such an "arrhythmia range" was denied by others (Lee *et al*) Similarly, the statement that concentrations of cyclopropane between 50 and 70 per cent. depress the hypothalamic centres responsible for ectopic arrhythmias (Thienes, Greeley and Guedel) and thus abolish them was not confirmed (Rait-Smith and Ostlere) A reflex origin of cyclopropane arrhythmias has also been assumed by several investigators (Seevers *et al*, Thienes *et al*) This view was based on the observation that atropine abolished the irregularities This argument seems to us unconvincing, for the ensuing tachycardia with the resulting shortening of diastole alone may suppress ectopic beats, and atropine in larger doses is known to have a direct effect upon the heart muscle where it inhibits impulse formation Experiments carried out with a different technique and interpreted as indicating a reflex origin of such arrhythmias were reported by Stutzman *et al* The only conditions in which we believe a reflex mechanism to have been responsible for ectopic arrhythmias observed in man under cyclopropane anaesthesia are those described by Reid and Brace (see chapter on "Nervous System", p 264)

All this tends to show that there is no agreement as yet about the mode of origin of ectopic arrhythmias occurring during cyclopropane anaesthesia The only point which can be considered established is that the anaesthesia should be lightened as soon as arrhythmias occur (Eversole, Sise and Woodbridge)

Other Drugs and Cyclopropane

Epinephrine enhances the formation of ectopic beats during cyclopropane anaesthesia (Meek, Hathaway and Orth) similar to its effect during chloroform anaesthesia In dogs, the intravenous injection of epinephrine in doses of 0 01 mgm per kg during cyclopropane anaesthesia caused ventricular tachycardia in eleven out of seventeen animals, whereas in seventeen control experiments epinephrine alone precipitated such arrhythmias only once (Meek, 1941) The rise of blood pressure is not the only mechanism responsible for the cardiac arrhythmias following cyclopropane and epinephrine (Moe *et al*), since compression of the aorta in dogs under cyclopropane anaesthesia does not cause arrhythmias (Murphy *et al*, 1949)

Ectopic arrhythmias caused by the combination of cyclopropane-epinephrine are [illegible] tioned by others (Orth *et al*, Meek 1941, Lee *et al*) Ectopic arrhythmias due to cyclopropane in dogs could be prevented by a prior injection of sodium amytal or pentothal sodium (Betlach) In a series of sixteen experiments on dogs prepared with nembutal no ectopic arrhythmias were observed during subsequent cyclopropane anaesthesia, not even with concentrations of the gas up to 75 per cent (Scherf, unpublished observation)

Other compounds stated to prevent such arrhythmias in dogs are yohimbine, ergotamine and procaine (Allen *et al*, Bennett, Dhuner and Orth) Inhalation of ether has been recommended with discontinuation of cyclopropane as soon as arrhythmias appear After the tissues have been saturated with ether it is claimed that renewed use of cyclopropane does not elicit arrhythmias (Milovsky and Rovenstine, cf also Johnstone)

The effect of procaine in such arrhythmias is discussed in the section on "Cocaine and Allied Compounds" (p. 309).

Clinical Observations

On the whole these are in agreement with experimental findings. Isolated ectopic beats occurring at first singly, then in increasing numbers, and ventricular tachycardia with multiform ectopic beats have been reported in man during cyclopropane anaesthesia (Kurtz, Bennett and Shapiro). This development closely resembles that during chloroform anaesthesia *A high degree of protection by the intravenous administration of barbiturates has* been reported, amounting, in the case of pentothal, to 90 per cent. (Guedel) The value of full doses of atropine in pre-medication for the prevention of arrhythmias during cyclopropane anaesthesia has recently been stressed by Rink, Helliwell and Hutton (*see* section on " Atropine "). Regarding the suppression of such arrhythmias by ether, *see* below, also section on " Ether " (p. 309).

Johnstone studied the heart rhythm electrocardiographically in ninety patients, anaesthetized with cyclopropane, with special reference to the presence or otherwise of hypoxia, CO_2 accumulation, and hyperventilation. He found that it was the accumulation of CO_2 which precipitated ventricular arrhythmias Hypoxia did not appear to have any influence on such arrhythmias. *They could be abolished by ether For their effective control the* effective elimination of CO_2 and avoidance of respiratory depression is recommended

Freeman saw ectopic ventricular beats occasionally during manipulation of the vagus in patients under cyclopropane anaesthesia.

While the occurrence of ectopic arrhythmias during cyclopropane anaesthesia can be considered established they do not occur invariably Waters found such arrhythmias in 2·22 per cent of cases with the patient in Plane I and in 12·72 per cent. with the patient in Plane IV. In a series of forty-one cases studied by Kurtz *et al*, such arrhythmias were observed in 10 per cent. Ziegler found extrasystoles and paroxysmal tachycardia in 10 per cent of 175 children with congenital heart disease and cyanosis submitted to the Blalock-Taussig operation under cyclopropane anaesthesia These arrhythmias subsided under ether and oxygen

The conditions favouring the occurrence of such cardiac irregularities are still obscure. An admixture of other hydrocarbons has been considered Cyclopropane is widely used to the great satisfaction of anaesthetist and surgeon In cardiac patients this type of anaesthesia is avoided by many and ether preferred Alimurung and Smith attribute the absence of serious cardiac arrhythmias in their series of ten patients, submitted to operation for coarctation, to the fact that cyclopropane was not used. Moreover, cardiac dilatation was observed to be caused by this compound (Brace *et al*). There is general agreement that in combination with cyclopropane the use of epinephrine and of allied compounds (pressor amines) is dangerous

SUMMARY

In man and in dogs cyclopropane causes ectopic arrhythmias in a considerable proportion of cases. In spite of extensive experimental work, some of which is briefly discussed, [illegible] The use of epin- [illegible] ;ventive effect are [illegible] g (*see* section on " Cocaine and Allied Compounds ").

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OTHER HYDROCARBONS

Propylene, which is an isomer of cyclopropane, has been investigated in experiments on cats and dogs (Caine and Reynolds). Ectopic beats originating in various foci in the ventricles were observed, they disappeared when the concentration of the gas was reduced. No extrasystoles were observed in nine experiments performed on one individual in whom this anaesthetic was used (Kahn and Riggs).

Trilene (trichlorethylene) belongs to the chlorinated hydrocarbons and in this respect is related to chloroform Though less toxic than carbon tetrachloride it is apt to cause ectopic arrhythmias (Geiger). Hewer (1941, 1943) studied fifteen cases during anaesthesia electrocardiographically and found auricular extrasystoles in one and ventricular ones in

two instances. He emphasized the frequent occurrence of auricular extrasystoles (Hewer, 1943). Frequent extrasystoles were also observed by others (Gordon and Shackleton, Hunter), but reports about the relative incidence of auricular and ventricular extrasystoles are conflicting. In an electrocardiographic study on forty patients (thirty males, ten females) Barnes and Ives found a great variety of arrhythmias. The incidence in per cent. of those due to ectopic beats was. auricular extrasystoles 12·5, ventricular 40, coupled beats 27·5, *multifocal ventricular contractions 15, multifocal ventricular tachycardia 10. These authors* found that, as a rule, ectopic arrhythmias occurred later—during the lower first or upper second plane—than other arrhythmias, though exceptions were observed They point out that arrhythmias giving the clinical impression of being due to auricular fibrillation were probably cases of multifocal ventricular tachycardia. This observation makes special care in the use of this anaesthetic imperative.

Isopropyl chloride (" Proponesin ") was found to produce pronounced arrhythmias, including multifocal ventricular extrasystoles, in healthy subjects and caused fatal cardiac arrest in a patient with thyrotoxicosis (Elam and Newhouse)

The effect of various hydrocarbons combined with epinephrine was studied by Chenoweth who investigated, in particular, benzene, heptane, gasoline (65 octane), butane and hexane All these compounds were found capable of sensitizing the mammalian heart for epinephrine to induce ventricular fibrillation The practical implication of these observations is that " apparently trivial accidents, quarrels and other disconcerting episodes may render an individual highly susceptible for some minutes to ventricular fibrillation if to the discharge of epinephrine is added exposure to the various substances described ". Aeroplanes and armoured vehicles, in which a combination of emotional stress and petrol fumes normally exist, are places *par excellence* where such accidents may occur by this mechanism. In a later study Garb and Chenoweth investigated the comparative effect of the hydrocarbons chloroform and benzene and the non-hydrocarbons ether, alcohol and acetone on the irritability of heart muscle (isolated papillary muscle preparation) and found that the former produced a marked increase in irritability whereas the latter were far less active. In a further series of experiments on cats these authors studied the relation of drugs affecting the sympathetic nervous system to the initiation of ventricular fibrillation It was found that during hydrocarbon inhalation (petroleum ether) epinephrine and *nor*-epinephrine produced ventricular fibrillation whereas N-isopropyl epinephrine, a purely inhibitory compound, failed to have this effect, though producing other arrhythmias. Dibenamine (3 mgm per kg), while not altering the vasopressor effect of 10 or 30 micrograms per kilogram of epinephrine, exerted a protective effect.

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authors' claim that the ectopic beats were of multifocal origin is not borne out by the reproduced electrocardiograms.

Ventricular extrasystoles were seen in one human case of acute benzol poisoning (Rossmann)

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ETHER

As compared with chloroform and cyclopropane, ether causes ectopic arrhythmias only rarely. This is true for experimental work as well as for clinical observations Regarding the former, in many hundreds of experiments we never observed ectopic arrhythmias in dogs anaesthetized with ether (with or without pre-medication with morphia) and can confirm similar earlier observations of Cluzet and Tixier, and of Caine and Reynolds. Not even when pressor amines were given did ectopic beats occur (Meek; Orth *et al*).

Some exceptions were reported, for instance in guinea pigs (Frommel) and in highly-trained dogs (Betlach).

In man, too, ectopic arrhythmias during deep ether anaesthesia are rare or absent (Cluzet and Tixier, Hill)

Whenever extrasystoles were observed they were of the supraventricular type (Meek). Kurtz, Bennett and Shapiro found auricular extrasystoles four times amongst twenty patients anaesthetized with ether.

The suppression by ether of ventricular arrhythmias during cyclopropane anaesthesia has repeatedly been observed (Milovsky and Rovenstine, Johnstone, *see* section on "Cyclopropane", Rink, Helliwell and Hutton whose paper is more fully discussed in the section on "Atropine"; Stein and Buchberg)

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COCAINE AND ALLIED COMPOUNDS

Experimental Investigation

The earlier observations that cocaine preparations applied to the epicardial surface may diminish the excitability of the heart as tested by mechanical or electrical stimuli and thus prevent the occurrence of extrasystoles (François-Franck 1892, Heitler 1898, Froehlich 1904, Kochmann and Daels 1908, Fauconnier 1908, Froehlich and Paschkis 1923) did not

attract much attention at the time, but became of increasing interest as thoracic surger[illegible] developed With the rise of cardiac surgery the importance of such compounds was furthe[illegible] enhanced since manipulation of the heart is apt to cause extrasystoles in operations fo[illegible] congenital heart disease or adhesions of the pericardium (Feil and Rossman, Stewart an[illegible] Bailey, Ziegler)

Mautz (1936) confirmed the earlier work that after the local application of cocaine o[illegible] meticaine on the epicardial surface of the heart the threshold for the production of extra-systoles by means of induction shocks was increased, and Beck and Mautz recommende[illegible] the intrapericardial injection of 2 cc of a 5-per-cent solution of procaine or meticaine i[illegible] order to reduce the risk of extrasystoles during operations on the heart.

Cocaine and related substances, if applied directly to the cardiac surface, cause im-mediate depolarization (Baron).

The intravenous administration of this group of compounds is the method most fre-quently employed at the present time for preventing extrasystolic arrhythmias durin[illegible] anaesthesia It has been demonstrated in experiments on dogs anaesthetized with chloro-form or cyclopropane that ventricular fibrillation resulting from the injection of epin-ephrine could be prevented by procaine or a similar compound, for example p-amino-benzoic acid (Hermann and Jourdan, Van Dongen, Shen and Simon, Burstein *et al.* 1940)

Ventricular fibrillation produced in dogs by the administration of benzol in combin-ation with adrenaline could also be prevented by the simultaneous injection of 8-10 mgm per kg. of novocaine (Shen). Even in the stage of ventricular tachycardia was procain[illegible] found effective in preventing ventricular fibrillation (Burstein *et al.* 1940) Reports abou[illegible] the action of intracardiac injection of this drug, once ventricular fibrillation had becom[illegible] established, are confl[illegible] rhythm[illegible] [illegible]. In the [illegible] ventri-cular fibrillation by faradization was increased According to Hirschfelder and Tamcales, procaine, pantocaine and nupercaine stop in dogs auricular fibrillation produced by faradiz-ation

Large doses of cocaine preparations are known to damage the heart: in the dog a[illegible] intravenous injection of cocaine or novocaine in a 2·5 or 5 per cent. solution may caus[illegible] right bundle branch block (Shookhoff), and focal application of cocaine to the sinus nod[illegible] produced sinus block and A-V rhythm (Hofmann; Rothberger and Scherf) Ventricula[illegible] tachycardia was observed by Tainter, Dock and Brown, and multifocal ventricular ectopic beats—precursors of ventricular fibrillation—were reported by Uhley and Wilburne It has, however, been pointed out by Doak and Selke that either the doses employed in these experiments were extremely high, or that the rate of injection was very fast If procaine is given by means of slow infusion and in smaller doses, as it is employed in clinical practice, the compound is quickly hydrolysed in the blood and the electrocardiographic changes are very slight

Regarding the recently introduced procaine amide, see below in this section.

Clinical Observations

In a small series (six) of healthy humans the intravenous administration of 1 g. of pro-caine (0 1 per cent. in physiological sodium chloride solution, given in the course of one to three hours) produced in the electrocardiogram only minor changes without any clinical significance (Doak and Selke).

In fourteen patients under a general anaesthetic the intravenous administration of 30–70 mgm. of procaine (in a 1 per cent. solution) abolished acute arrhythmias, often dramatically (Burstein, 1946). No untoward effects were observed regarding respiration or

central nervous system. Fraser and Kraft found a combination of pentothal and procaine effective in preventing irregularities due to cyclopropane. Barbour and Tovell successfully employed a slow intravenous infusion of a weak solution of procaine as a preventive (1,000 cc of a 0·1 per cent solution infused within one hour) Bittrich and Powers used a 1 per cent. solution, giving it as a continuous intravenous infusion in seventeen cases In five instances extrasystolic arrhythmias occurred in spite of such infusion being given at a rate of 60–100 drops per minute and in one case it was found necessary to increase the rate of flow to 150 drops per minute. In two patients procaine precipitated convulsions Schaffer, Steinman and Scherf studied the effect of procaine on various arrhythmias One group of eleven patients received an intravenous drip of 300–500 mgm procaine hydrochloride, given in a 0·1 per cent saline solution in the course of 8–30 minutes A second group of twenty-one patients were given 100 mgm by means of a rapid intravenous injection (10 cc. of a 1 per cent solution injected within about four seconds) The effect on extrasystoles (ventricular, seven, auricular, five cases) was disappointing In three cases the drug precipitated extrasystoles In auricular flutter the decrease in auricular rate may result in an increase of the ventricular rate, owing to a greater number of impulses being conducted (akin to similar observations made with quinidine) In the doses given it proved a safe though rather ineffective procedure

Recent reports on the usefulness of procaine in combating cardiac arrhythmias during thoracic surgery are more optimistic. Thus Ziegler, in a series of 175 children with cyanotic and twenty with acyanotic congenital heart disease submitted to operation, encountered premature contractions in twenty-three and paroxysmal ventricular tachycardia in three instances and mentions procaine amongst the measures to stop multiple extrasystoles and ventricular tachycardia Burstein *et al* (1949) studied cardiac arrhythmias electrocardiographically in thirty-three cases submitted to thoracic surgery for various conditions Ectopic arrhythmias were found to be pronounced in the three instances of pericardiectomy during manipulation of the pericardium, for their suppression the authors recommend the topical application of a 2-per-cent solution of procaine as well as the rapid intravenous injection of 100 mgm of this drug in a 1- or 2-per-cent solution Taylor *et al*, using a 1-per-cent solution of procaine and starting with 40 mgm per minute in adults, concluded that procaine is "relatively effective in preventing cardiac arrhythmias during intra-thoracic operations with cyclopropane" They warn against too rapid administration after starting These conclusions are based on 211 administrations, mainly in thoracic operations, no electrocardiograms were taken

An unusual observation has been reported by Lampson, Schaeffer and Lincoln, concerning a seven-year-old boy operated upon for laceration of a foot The patient had premedication with morphia and atropine, also seconal, anaesthesia was inducted with cyclopropane and continued with ether After the operation was finished ventricular fibrillation suddenly occurred Artificial respiration was given, the chest opened and the heart was massaged after intracardiac injection of 3 cc. of a 1-per-cent. solution of procaine, followed by a second injection of 2 cc The fibrillation stopped and the boy recovered

Untoward effects and even fatal accidents have been reported as a result of novocaine and allied compounds. In some instances they were due to overdosage, in others to hypersensitivity of the patient Sensitivity to this group of drugs varies considerably amongst [illegible]

untoward effects in a patient a spray on the nasal mucous membrane of 20 per cent novocaine with 10 minims per ounce of adrenaline 1 : 1,000 resulted in bundle branch block with multifocal ventricular extrasystoles (Young and Glauber)

Notwithstanding such observations it can be said that the administration of procaine in doses of 300 mgm. given slowly by intravenous infusion in the course of twenty to t minutes, or of 100 mgm. given by rapid intravenous injection within a few seconds is a procedure.

Procaine is hydrolysed in the human body into p-amino-benzoic acid and diethylam ethanol The effect upon arrhythmias of the latter was investigated by Rosenberg e and the compound found fairly effective in suppressing in man ventricular extrasystoles tachycardias, but not auricular ones It was, however, less effective than procaine and d employed were 0 5–5 grammes intravenously in a 11·2-per-cent aqueous solution. In diethylaminoethanol prevented ventricular tachycardia induced by epinephrine du cyclopropane anaesthesia (based on Meek, Hathaway and Orth) and was the only compo of two homologous alcohol series, tested in this respect, to do so in non-toxic doses (M Lott, Cooper and Brodie).

In a search for a drug possessing the activity of procaine without its toxicity var esters of diethylaminoethanol were examined for stability and for their efficacy in preven the epinephrine-induced ventricular tachycardia in dogs under cyclopropane anaesth The most promising compound to date is the amide of procaine (N'-(2-diethylaminoetl p-aminobenzamide) (Pronestyl) which is unaffected by the enzyme responsible for the r hydrolysis of procaine and which, in therapeutic doses, does not produce central stimulat This drug is also effective by mouth (Mark, Berlin *et al.*). According to a recent re (Kayden, Brodie and Steele) it was tried in fifty-five patients with ventricular extrasyst and, administered either orally or intravenously in doses of 0 4 to 1·0 gramme, suppre the ectopic beats for a period varying from a few minutes to many hours It proved pa cularly effective in controlling ventricular tachycardia, which was terminated in four out of sixteen patients by this drug, given orally, intravenously, or by both routes. Amo these were eight who had myocardial infarction and seven in whom quinidine in large d had been unsuccessful With oral administration hypotension, which is observed a sometimes serious side-effect during intravenous administration, did not develop and the route is therefore the method of choice. The effective oral dose was found to vary widel different patients An initial dose of 1·25 grammes followed in one hour by an additic 0 75 gramme, if the tachycardia persisted, proved adequate in the majority of cases, bu necessary subsequent doses of 0 5–1 0 gramme every two hours may eliminate the arrhy mia In some cases the exhibition of the drug is necessary for a longer period in orde prevent the recurrence of extrasystoles or ventricular tachycardia; the suggested maint ance doses range from 0·5 to 1 0 gramme every three to six hours. In cases in which drug has to be given intravenously it should be given slowly (100 mgm /minute or less) blood pressure and electrocardiogram continually observed. Good results with Prone in the suppression of ventricular ectopic arrhythmias were also reported by Diaz Cabrera, Kinsman *et al.*, and Berry *et al*

A recent experimental study of Harris *et al.* showed that the rate of ectopic ventricu arrhythmias elicited in dogs by his method of occluding a coronary branch (p 421) markedly reduced by procaine amide. Complete abolition of ectopic activity was seen o exceptionally, but the ectopic rate became so slow that the risk of ventricular fibrillati was practically eliminated Furthermore, the marked reduction in ectopic rate resulted a great improvement in dynamic efficiency of the heart. In instances of low frequen ectopic rhythms the effect of Pronestyl was variable and unpredictable. (Procaine, admin tered intravenously, had either no or only a very transient suppressor effect on such ecto rhythms.)

Recently this compound has also been successfully employed for the suppression "multiples arhythmies ventriculaires" precipitated by cardiac catheterization (injection 5–9 ml. of a 10-per-cent. solution through the catheter, van den Heuvel-Heymans)

While Pronestyl seems to be a definite advance in the treatment of ventricular extrasystoles and tachycardias, its effect on auricular arrhythmias, while not as firmly established at the moment, seems to be promising (Schlachman *et al*, Berry *et al*) Schaffer, Blumenfeld, Pitman and Dix found that an intravenous injection of 600 mgm abolished auricular extrasystoles for several hours and converted auricular paroxysmal tachycardia, flutter and fibrillation into sinus rhythm As already mentioned, the intravenous injection has to be given [illegible] produced nausea, diarrhoea and headache. Schaffer made a quantitative comparison between the anti-arrhythmic potency of procaine amide and quinidine in cases with persistent auricular and ventricular extrasystolic arrhythmias. He found that, weight for weight, quinidine is approximately four times as strong as procaine amide For every grain of quinidine necessary to obtain a certain therapeutic effect 0 25 gramme of Pronestyl was found necessary In his experience the intravenous injection of Pronestyl is superior to quinidine, the usefulness of procaine amide given by mouth is limited by nausea and vomiting

Observations on larger numbers of cases must be awaited before the value of this most recent drug can be assessed more definitely Our provisional opinion is that procaine amide is very useful in ventricular extrasystoles and ventricular tachycardias after coronary occlusion, in such cases it may be life-saving, since not infrequently such patients do not respond to quinidine In addition, Pronestyl is helpful in instances of intolerance to quinidine which are by no means rare Its application in auricular arrhythmias seems promising

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BARBITURATES

Barbiturates, even if given intravenously, do not affect cardiac function in any appreciable way provided the dose is small, the heart in good condition and the injection given slowly. Larger doses have a depressant effect, the diminished excitability causing ectopic beats to disappear

Experimental

Ectopic arrhythmias produced in a variety of ways have been reported to be abolished, reduced or prevented by barbiturates. *A few examples may be quoted*

In cats, Dikshit found a great reduction, by sodium barbitone, in the number of ectopic beats produced by clamping of the carotid arteries or by intracerebral (ventricular) injection of caffeine (*see* also p 268) Braun and Samet observed, also in cats, that the intravenous injection of 0 1–0 15 gramme per kg. of Luminal-sodium increased the threshold for faradic currents to cause ventricular fibrillation This was confirmed for cats and dogs by van Dongen who also found that luminal abolished ectopic arrhythmias precipitated by epinephrine and by barium chloride Similarly, such arrhythmias resulting from ephedrine were prevented in dogs by an injection of sod barbital given 125–200 minutes before that of ephedrine. This effect was attributed to a partial vagal paralysis and to a central depressant action on automatic centres (Meek and Severs).

The action of barbiturates on arrhythmias due to cyclopropane, where they were claimed by some to be an effective depressant, is discussed in the section on " Cyclopropane ".

While barbiturates do not cause arrhythmias (Gruber; Hafkesbring and MacCalmont), thio-barbiturates are known to have this effect; if given intravenously in dogs, 10 mgm may cause ventricular bigeminy (Gruber). Following an intravenous injection of sodium thiopentobarbital ectopic beats occurred after a latent period of six minutes This was confirmed in dogs, cats and rabbits by Kohn and Lederer who did not, however, find such arrhythmias in five monkeys after the intravenous injection of pentothal.

Clinical Observations

Clinical observations on the effect, upon arrhythmias, of barbiturates are few Dikshit studied a patient with numerous extrasystoles occurring at regular intervals, within thirty minutes of being given 1 gramme of sodium barbiturate by mouth the number of extrasystoles had become reduced by half, this effect lasting for two hours

Regarding thio-barbiturates, no extrasystoles were seen in seventeen patients after the intravenous administration of such compounds (Volpitto and Marangoni) Extrasystoles are not a feature in patients anaesthetized with pentothal (which is a thio-barbiturate) (Kohn and Lederer)

SUMMARY

Barbiturates tend to abolish, prevent, or diminish the number of ectopic beats caused in various animals by various methods; this holds good particularly for the arrhythmias resulting from clamping of the carotid arteries, from cyclopropane, epinephrine or ephedrine. Similar conditions seem to prevail in man, but the number of clinical observations is inadequate for forming a definite opinion.

Thio-barbiturates cause ectopic arrhythmias in certain animals, but do not exert such effect in man

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SALICYLATES

Experimental

Only very few experimental observations on the incidence of extrasystoles after administration of salicylates have been reported No such arrhythmias were found in the isolated heart of the frog and turtle (Salant and Johnson) and in the heart *in situ* of rabbits (Renz).

Clinical Observations

Lommel described in 1902 extrasystoles during administration of salicylates in a patient with pyrexia and pleurisy and considered the possibility that the arrhythmia may have been due to the drug Subsequently, similar observations have repeatedly been reported, particularly in patients with rheumatic fever (Leconte; Danielopolu; Bass, Marchal and H. de Balsac, Laubry) Leconte had the impression that extrasystoles were particularly prone to occur after prolonged salicylate treatment and considered their presence as a sign of saturation of the body with the drug

In hardly any of these investigations has any evidence been put forward that the ectopic beats actually were due to salicylates and were not caused by the underlying disease for which the patient was given salicylate treatment. The position is somewhat reminiscent of that regarding A-V block occurring during salicylate treatment of patients with rheumatic fever in the past this had frequently been attributed to the drug until the true situation was established, namely, that the disturbances of conduction were never due to the drug, but a common sign of the disease

The only case which is somewhat suggestive is the isolated observation of Danielopolu on a boy of seventeen with rheumatic fever In this case extrasystoles occurred during the exhibition of salicylates, disappeared when medication was discontinued, to re-appear when the drug was re-instituted

SUMMARY

We concur with the view expressed by Parkinson *et al* that the precipitation of extrasystoles by salicylates cannot be considered established and that, to say the least, it is doubtful whether salicylates produce such arrhythmias.

REFERENCES

EPINEPHRINE (ADRENALINE), EPHEDRINE AND ALLIED PRESSOR AMINES

Epinephrine is one of the most important compounds regarding the production of ectopic arrhythmias and this is true for the physiological as well as the clinical aspect. The arrhythmias resulting from epinephrine in association with other drugs are of paramount importance Those occurring during chloroform and cyclopropane anaesthesia, and in association with various hydrocarbons, are discussed in some detail in the appropriate sections to which the reader is referred as well as to the chapter on "Extrasystoles and the Nervous System"

Experimental

Epinephrine

Arrhythmias occurring at the height of the action of epinephrine were noted early in experimental work, but since at the time such irregularities were only recorded by means of blood-pressure tracings a more detailed analysis of the types of arrhythmia is not possible

An early electrocardiographic study by Kahn (1909) showed ectopic beats in the dog following the intravenous injection of 0 1 mgm of epinephrine Subsequently, Levy pointed out that, in these experiments, chloroform was used as anaesthetic and maintained that this was responsible for the arrhythmia After severing the vagi ectopic beats occurred less frequently or were absent (Kahn) This was confirmed by Nobel and Rothberger who also found that after vagotomy or the administration of atropine larger doses of epinephrine were necessary to precipitate ectopic beats, and that they occurred less frequently It is probable that the sinus tachycardia, resulting from vagotomy or the administration of atropine, was one of the factors accounting for the rarer occurrence of the arrhythmia A direct depressant effect of atropine certainly also plays a part (*see* section on "Atropine") Nobel and Rothberger also reported that during ether anaesthesia epinephrine caused ectopic beats in the dog whereas, according to Meek and Seevers, ephedrine does not have this effect in similar circumstances In this connexion, too, the part played by sinus tachycardia should be considered which, in the case of ether, results from peripheral vagal paralysis In Egmond's experiments on the automatically beating perfused heart of the dog no ectopic arrhythmias were observed, but in his investigations the excitability of the heart can hardly be assumed to have been normal

In cats and rabbits premature beats were invariably seen after the administration of epinephrine (Petzetakis, Schlapp) In the experiments of Hoff and Nahum on cats the intravenous injection of 0 1–0·2 mgm of epinephrine consistently caused ectopic beats

effect is eliminated by an equalizer (Allen). Denervation of the carotid sinus or severing of the depressor nerves in dogs did not abolish the arrhythmia caused by epinephrine (Milles and Smith).

Ectopic beats could be elicited by epinephrine with greater constancy and in greater numbers if the animal had previously been sensitized by small doses of barium (Rothberger and Winterberg) In such experiments the action of epinephrine was akin to that of faradic *stimulation of sympathetic cardiac nerves. An entirely different effect of epinephrine* was observed if the animal had previously been treated with aconitine in such small doses that, except for the occurrence of extrasystoles, no changes in cardiac function occurred: in such circumstances extrasystoles in bigeminal rhythm invariably disappeared on stimulation of the sympathetic cardiac fibres and epinephrine had the same effect (Scherf, unpublished observations). (*See also* chapter on " Extrasystoles and the Nervous System ".)

According to Wégria and Nickerson, epinephrine raises the fibrillation theshold in the dog.

Epinephrine also increases the automaticity of excised strands of Purkinje tissue of the dog's heart, as ascertained by microscopic observation (Ishihara and Pick, Wachstein)

Regarding the effect of barbiturates on arrhythmias produced by epinephrine, *see* section on " Barbiturates " (p. 315)

Ephedrine

In dogs, 5–10 mgm. per kg given intravenously cause only slight changes in the T waves; larger doses (20 mgm. per kg) have a depressant effect on the specialized tissue (Chen and Meek) The latter mode of action, which is characteristic for ephedrine, is presumably the reason for the rare occurrence of dangerous arrhythmias in instances in which ephedrine is employed La Barre confirmed in cats the depressant effect of ephedrine in doses exceeding 20 mgm per kilo and did not see arrhythmias if doses up to 50 mgm per kilo were given intravenously to cats in deep chloroform anaesthesia According to Melville ephedrine, unlike epinephrine, never induces ventricular fibrillation during chloroform anaesthesia. As mentioned above (p 317), ephedrine, as distinct from epinephrine, does not produce ectopic beats in dogs anaesthetized with ether Regarding the prevention by sodium barbital of ectopic arrhythmias resulting from ephedrine, *see* section on " Barbiturates " (p. 315)

Clinical Observations

The occurrence of extrasystoles is a common experience in patients who use epinephrine in the usual doses for such conditions as bronchial asthma, allergic conditions, etc If extrasystoles were already present before, their number is increased by epinephrine. Bourne investigated this subject in some detail by giving subcutaneously 1 cc. of a solution of 1 · 1,000 to eighteen patients with persistent extrasystoles; electrocardiograms were taken for one minute every five minutes The results were uniform · about five minutes after the injection the number of extrasystoles increased considerably for thirty to sixty minutes, while the increase in the heart rate was slight. Patients with auricular extrasystoles developed ventricular ones and vice versa, additional centres of ectopic impulse formation being activated by the drug. According to Frey, 0·3 mgm of epinephrine injected into normal subjects elicited extrasystoles in 9 per cent.

[illegible] (Hoffmann; [illegible] of [illegible] les [illegible] by

Byrd: in a patient anaesthetized with ether focal application of epinephrine was followed by severe arrhythmias and fall in blood pressure. It is probable that the epinephrine, and

not the ether, was responsible for the accident since, according to the author, "a large pack" soaked with epinephrine in a 1 : 1,000 solution was applied to a bleeding area during the operation

In patients with A-V block and Adams-Stokes' attacks due to transient ventricular fibrillation the administration of small doses of epinephrine may cause ventricular extrasystoles (Roelsen) and ventricular fibrillation (Danielopolu and Danulescu 1916, Dock, Schwartz and Jezer)

In patients with suprarenal tumours enhancement of impulse formation has been observed during hypertensive crises, attributed to adrenaline circulating in the blood This seems to affect mainly impulse formation in the A-V node, with resulting A-V rhythm and various forms of dissociated rhythms, including dissociation with interference (Burgess, Watermann and Cutts, Hegglin and Holzmann, Espersen and Jorgensen) In Hegglin and Holzmann's patient occasional ventricular extrasystoles were also observed during such crises

Quinidine and acetyl-beta-methylcholine abolish epinephrine extrasystoles (Hoff and Nahum, Nathanson 1935, 1936)

In addition to epinephrine other pressor amines were studied Veritol caused auricular or ventricular extrasystoles and short attacks of paroxysmal tachycardia in eight out of thirty patients (Aschenbrenner and Codas-Thompson) Intravenous injection of paredrine also precipitated extrasystoles (Iglauer and Molle)

SUMMARY

It has frequently been demonstrated that pressor amines, in particular epinephrine (adrenaline), cause ectopic beats and paroxysmal ventricular tachycardia in various species If the administration of such drugs was associated with chloroform or cyclopropane anaesthesia, or if the animals had previously been given barium, ectopic beats occurred in great numbers and such arrhythmias tended to develop into ventricular fibrillation If, on the other hand, aconitine had previously been given, the ectopic beats were abolished by epinephrine Ephedrine, owing to its depressant effect, causes ectopic beats more rarely

Clinical observations are in accordance with the experimental ones even after the exhibition of small doses of epinephrine, as they are commonly employed in clinical practice, extrasystoles are frequently observed and auricular as well as ventricular fibrillation has occasionally been reported On the other hand, epinephrine may also abolish extrasystoles, this effect is not only due to tachycardia

The greatest caution is necessary if pressor amines are given during chloroform or cyclopropane anaesthesia

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... dine on fibril-

STRYCHNINE

Though the use of strychnine in the treatment of extrasystoles has repeatedly been recommended its efficacy is doubtful and reports about its effect are conflicting

The idea of employing strychnine in this way seems to go back historically to the time at which extrasystoles were believed to be due to weakness of the heart muscle, the arrhythmia indicating the difficulties of the heart muscle in contracting against aortic pressure.

... gramme, *see* section on "Treatment", p. 477), was due to Wenckebach who credited his English friends with having given him this suggestion (Wenckebach, 1938)

Experimental

According to Smith (1917), in the heart of frogs and rabbits strychnine acts as a depressant and retards the occurrence of arrhythmias due to aconitine, ouabaine and coronary occlusion. From these experiments, which do not appear to have been repeated, Smith concluded " with the greatest reserve " that strychnine may have a place in the treatment of ectopic beats.

Clinical Observations

In a critical review on the action of strychnine in heart failure Parkinson and Rowlands arrived at the conclusion that there is no justification for the use of this drug

For the treatment of extrasystoles several investigators found strychnine effective (Walsh, Fahr). Carter and Traut used a combination of 3 grains of quinidine sulphate and 1/30 of a grain of strychnine sulph In a sixty-year-old patient with frequent extrasystoles neither digitalis nor quinidine or strychnine alone in the above doses proved satisfactory. The best effect on the extrasystoles was achieved when quinidine and strychnine were given combined

In a case of aortic regurgitation with extrasystoles strychnine repeatedly abolished the premature beats which recurred whenever the drug was discontinued. As no other drug was given this is perhaps the most convincing observation of a beneficial effect of strychnine on extrasystoles (Wenckebach)

On the other hand Smith (1924) reported two instances in which strychnine precipitated extrasystoles.

CONCLUSIONS

The number of controlled observations on the effect of strychnine on extrasystoles is too small to warrant any definite views The impression obtained by perusal of the relevant literature is that the efficacy of strychnine in the treatment of such arrhythmias is highly questionable

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CAFFEINE

Experimental

It may be of some historical interest to mention that as early as 1872 Aubert reported arrhythmias in dogs following the intravenous injection of 0·1 gramme of caffeine Since only blood-pressure tracings were recorded the kind of arrhythmia could not be analysed. Aubert quoted older observations of Lehmann regarding irregular and intermittent pulse in man after ingestion of 0·3–0 6 gramme of caffeine.

Following the administration of caffeine Pilcher observed ectopic beats in dogs, *but not* in cats Beattie, Brow and Long, and Dikshit, who reported their occasional occurrence in cats as a result of caffeine, showed that they were due to a direct action of this drug upon the hypothalamic centres. In earlier experiments in dogs, carried out on the perfused heart

in situ, in which complete A-V block had been produced, Egmond found that caffeine precipitated ectopic beats which gradually increased in number, the arrhythmia culminating in an attack of ventricular tachycardia. In these experiments a direct action on the cardiac centres has also to be assumed.

Clinical Observations

That the consumption of coffee or tea may produce extrasystoles is a common clinical experience and, in many textbooks, these beverages are rightly mentioned as important and frequent causes of extrasystoles. Some reports of these irregularities, then described as intermittent pulse, can be found in writings published long before the modern classification of arrhythmias (for example, Stokes 1854, Lorain 1870, Riegel 1877). Mackenzie described a case in which extrasystoles occurred after every cup of tea consumed. Even the time of day at which tea is taken may determine whether or not extrasystoles are precipitated (*see* section on " Treatment ", p 473) The disappearance of the ectopic beats once the beverage is discontinued demonstrates that, in such cases, it actually was the cause of the arrhythmia.

Very occasionally caffeine seems to exert the reverse effect, that is, abolishes ectopic beats Such an observation was reported by Barton, regarding caffeine sod. citr. given in doses of 3 grains, thrice daily

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NICOTINE

Experimental

Reports about the effect, upon ectopic impulse formation, of nicotine are conflicting. According to Clerc and Pezzi, the intravenous injection of 0·1–0 2 mgm. per kg. of nicotine in dogs occasionally causes ectopic beats which usually are auricular in origin. In one experiment a bigemina rhythm, and on one occasion trigeminy was observed In view of the rarity of spontaneous extrasystoles in dogs these findings may be of some significance Other investigators were unsuccessful in their attempts to elicit arrhythmias, by nicotine, in cold-blooded animals or in the mammalian heart (Barry, Frommel).

In experiments in which the animals were sensitized for the development of ectopic arrhythmias results were more consistent In dogs sensitized with barium Rothberger and Winterberg found that nicotine elicited such arrhythmias, its effect resembling, in this respect, that of epinephrine or of faradic stimulation of the cardiac sympathetic. Similarly, A. G Levy reported ventricular fibrillation in cats resulting from nicotine during light chloroform anaesthesia; its occurrence was independent from any vagal mechanism.

Clinical Observations

Reports about the occurrence of intermittent pulse after smoking, and attributed to it, go back a considerable time (Graves and Stokes 1827, Lorain 1870, Nothnagel 1876, Riegel 1877) Regarding the amount of smoking which is necessary to produce extrasystoles reports are conflicting (Grassmann; Gallavardin; Boas and Levy) On several occasions observations were reported in which extrasystoles occurred during smoking, disappeared while it was discontinued, to re-appear again when smoking was resumed (Bickel, Leconte)

By smoking two or three cigarettes, Goodall could produce extrasystoles in himself and, according to this observer, during the First World War abuse of smoking seems to have been a recognized method of producing extrasystoles in order to evade military service. Kulbs reported that smoking causes extrasystoles more frequently in young people while in the elderly it is more apt to produce anginal pain

In a study on fifty-five cases on the effects of nicotine intoxication, on the other hand, Genkin, Piskarew, Serebrjanik and Braun observed auricular extrasystoles in only three, and ventricular ones in two instances It is also noteworthy that in a recent electrocardiographic study in forty-six subjects (eighteen normals, twenty-four patients with coronary, four with peripheral vascular disease) on the effect, upon the circulation, of the intravenous injection of 2 mgm nicotine bitartrate extrasystoles are not even mentioned (Boyle, Wégria, [illegible] tine and smoking in producing arrhythmias; which should be some comfort to inveterate smokers.

SUMMARY

[illegible]

extrasystoles has yet been demonstrated

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ACONITINE

There is hardly any other drug which experimentally is apt to produce cardiac arrhythmias so constantly as aconitine (Matthews; Cash and Dunstan; Cushny). In such experiments ectopic beats occurred a short time after the administration of minute doses of the drug, soon followed by ventricular fibrillation.

A detailed electrocardiographic study demonstrated such arrhythmias to be due to auricular or to ventricular multiform ectopic beats (Dasbach, working in Einthoven's laboratory)

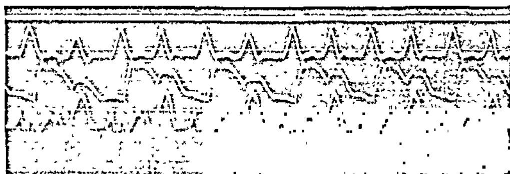


FIG 168 —From an experiment on a dog Tracings from above downward indicate suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base 0 02 second. Bigeminal rhythm owing to one ventricular extrasystole following each supraventricular beat, produced by aconitine The extrasystoles have constant shape and accurate coupling

Subsequently it was shown in dogs that, with careful intravenous administration of aconitine and repeated vagal stimulation, bigeminal heart action, persisting for over one hour, could be produced with great constancy The bigeminy was due to extrasystoles, auricular or ventricular in origin, which in the electrocardiogram showed constancy of shape and of coupling (Scherf, 1929) This method made it possible experimentally to [illegible]

More recently it has been established that focal application of 0 05 cc. of a 0 05-per-cent. solution of crystalline aconitine, in the form of a subepicardial injection into the dog's auricle, is followed by a prolonged regular auricular tachycardia with a rate of about [illegible]

This auricular tachycardia showed a marked increase of rate during vagal stimulation and in rare cases auricular fibrillation developed. If the same amount of aconitine was injected near the head of the sinus node into the *taenia terminalis* auricular fibrillation often appeared (Scherf, Romano and Terranova) In these studies it was possible to produce auricular arrhythmias, by aconitine, without additional vagal stimulation, either faradic or by vagomimetic drugs, and they could thus be investigated without the complications inevitably created by additional interferences The result of these investigations also made it possible to form an opinion about the nature of such auricular tachycardias, in particular whether they should be considered as paroxysmal tachycardia or as auricular flutter, and seem to have an important bearing on the acceptance or rejection of the theory of circus movement as accounting for the mechanism underlying auricular flutter and fibrillation (*see* p 223)

That impulse formation in isolated strands of Purkinje tissue is enhanced by aconitine was shown by Ishihara and Pick, and by Wachstein

Regarding the effect of the topical application of aconitine to the *ventricle*, see sections on "Flutter and Fibrillation", p 232, and on "Atropine", p 333.

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VERATRINE

Veratrine is a mixture of several veratrum alkaloids contained in various species of liliaceous plants Recent work has considerably advanced our knowledge of the chemical composition and biological action of individual alkaloids This whole problem has been comprehensively reviewed by Krayer and Acheson in 1946

Regarding the action of these compounds upon the circulatory system, investigations were mainly concerned with their effect on blood pressure and heart rate, whereas that on ectopic impulse formation has attracted less attention There are, however, several investigations the results of wh[illegible]ch have a bearing on the latter probl[illegible]

Experimental Investigations

"Extra[illegible]
reporte[illegible]
allow d[illegible]

Seemann and Victoroff found " Wuhlen " of the frog's heart in the late stages of veratrine poisoning. Their tracings show ectopic ventricular rhythms and some are suggestive of ventricular flutter and fibrillation. Ectopic rhythms are also suggested by tracings of subsequent papers by this group of workers (Kretzer and Seemann, Seemann). Wachstein, optically recording the contraction of Purkinje fibres of the dog's heart, interpreted his records as indicating bigeminal rhythm, often with constant coupling of the smaller beat, the extrasystoles displacing the dominant rhythm and sometimes being interpolated. Gibert-Queraltó and Pescador, recording in dogs electrocardiograms and suspension records, reported extrasystoles with fixed coupling, but their tracings can be better interpreted as

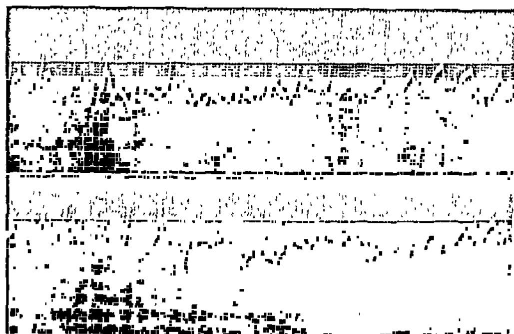


FIG [illegible] strips are con- [illegible] t-ventricular [illegible] Note slow [illegible] absence of [illegible] on, see text.

showing ectopic ventricular rhythms. Some records believed by those authors to demonstrate bigeminal rhythms with extrasystoles occurring very late in diastole (prematurity of only 0 01 second) seem more likely to indicate alternation of intraventricular conduction

Soaje Echague found in dogs and rabbits that extrasystoles (usually multiform ventricular) occurred at the stage of hypertension, but does not reproduce any tracings Terminal ventricular fibrillation was observed in dogs, but not in rabbits.

In strips of the left auricle of the heart of guinea pigs Rothberger and Sachs found that 0·7 mgm. of veratrine in a 1 : 1,000 solution in divided doses invariably precipitated rhythmic activity of high frequency, up to 360, but that this response was only transient and was soon followed by contracture. If, however, by changing the nutrient fluid, veratrine was removed at the start of such rhythmic activity, this persisted up to four-and-a-half hours, arrhythmias being common Awakening of rhythmic activity by veratrine was also found in strips of ventricles of the turtle's heart (Rosenblueth *et al*).

There is therefore no doubt that veratrine alkaloids can precipitate ectopic rhythms. The underlying mechanism is intimately related to the property of such compounds to increase and prolong the negative after-potential. The relation between negative after-potential, supernormal phase of recovery and repetitive response to single or continuous stimuli is discussed in more detail in the chapter on " Mechanism ". Suffice it to say here that, in connexion with veratrine, such relations were established in nerve by Graham and Gasser. Goldenberg and Rothberger showed in Purkinje fibres of dogs' hearts that veratrine in higher doses produced abnormal rhythms very akin to tachycardic attacks whereby the rapid impulses followed an initiating beat during its greatly prolonged after-potential, their paper is discussed in some more detail in the chapter on " Mechanism " (p 502) Observations on the effect of veratrine upon nerve were also important in showing that the negative after-potential, though a very important factor, is not the only one to account for supernormality Such findings are discussed in the review by Krayer and Acheson

None of the papers discussed have provided any evidence that in the heart extrasystoles in the strict sense of the term are produced by veratrine alkaloids Recently, Scherf and

interference between sinus and an ectopic rhythm Fig. 169 provides an example. It shows parasystole with interference between S-A and an ectopic left-ventricular rhythm. The sinus beats have slender, high and peaked P waves which are easily identified, followed by R waves which vary in height and inverted T waves The initial deflections of the ectopic beats have deep S waves which are followed by upright T waves. The cycle length of the sinus rhythm is 0·40 second (rate: 150 per minute), that of the ectopic rhythm 0 38 second (rate: 158 per minute). Owing to the close proximity of the rates of these two rhythms, a slow shift between them occurred Combination beats were also recorded, for example, the third and fourth but last complexes

The main difference between such experimental parasystole and that observed in clinical instances was that in the experimental variety the ectopic rate was much faster. If several such parasystolic foci were produced in different portions of the heart interferences of several rhythms ensued It is of interest that extrasystoles with accurate coupling were never observed in these experiments, this is the more noteworthy as true extrasystoles can readily be elicited by the topical application of digitalis or strophanthin, that is, by compounds with which veratrine has often been compared regarding some of its biological actions

Stutzman *et al* found in dogs anaesthetized with pentobarbital that the intravenous injection of 20–50 times the minimal effective dose of Veriloid produced *inter alia* transient A-V rhythm, and still larger doses ventricular tachycardia, at 200–500 times the minimal dose a coarse ventricular fibrillation was occasionally observed In the unanaesthetized animal very high intravenous dosage produced similar effects except that ventricular fibrillation

according to its vasodepressor effect in dogs It does not contain several of the powerful identified alkaloids (Kauntze and Trounce, 1951a)

Clinical Observations

In studies reported so far on the treatment of hypertension with Veriloid, arrhythmias

mation may become important.

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CHOLINE AND DERIVATIVES

Experimental Investigations

Of this group of drugs, acetylcholine is the most important and most widely studied. Regarding its action on the heart, its direct stimulating, "nicotinic"—as distinct from its parasympathomimetic, "muscarinic"—effect has attracted increasing attention of late.

Most of such investigations are concerned with the effect of acetylcholine upon the contractility. Regarding studies on the effect of this compound and its derivatives upon ectopic rhythms, which alone are relevant in the present context, data are available which tend to show that they may suppress as well as precipitate such arrhythmias.

A pronounced *inhibitory* effect of acetyl-beta-methyl-choline upon ventricular rhythms produced by adrenaline has been established by several authors (Hoff and Nahum, Nathanson 1935, 1936).

The *stimulating* effect has attracted increasing attention in connexion with the rôle played by acetylcholine in the transmission and initiation of impulses in various tissues (for example, sympathetic ganglia, Bronk; sensory nerve endings, Gray). In the heart, such stimulating effect has been reported in a variety of experimental conditions.

If, in experiments on dogs with the heart *in situ*, such small doses of aconitine were injected that no changes in the electrocardiogram occurred, the intravenous injection of choline or acetylcholine precipitated extrasystoles. This effect was not abolished by atropinization (Scherf 1929, *see also* section on "Aconitine" and chapter on "Nervous System"). A stimulating effect upon ectopic impulse formation in the dog's heart was also seen by Hall, by Noth, Essex and Barnes, and by McDowall, also by Goldenberg and Rothberger in isolated Purkinje fibres, and by Garcia Ramos and Rosenblueth in the isolated appendage of the dog's auricle.

The starting point of Burn's studies on the stimulating effect of acetylcholine was the

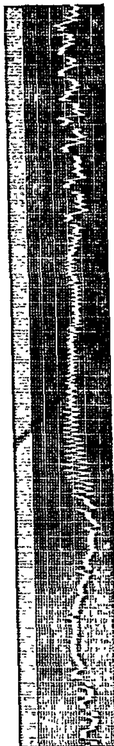


FIG 170.—From an experiment on a dog Auricular flutter and fibrillation immediately precipitated by the topical application to the sinus node of acetylcholine during vagal stimulation Note, in the beginning of the record, the inhibiting effect upon A-V conduction of the vagal stimulation before acetylcholine was subsequently applied by means of a filter paper moistened with a 5-per-cent solution

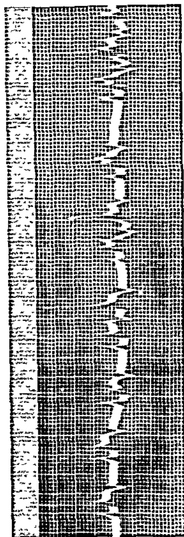


FIG. 171.—From an experiment on a dog, weighing 12 kg, five minutes after the intravenous injection of 1 2 mgm of atropine sulphate Auricular extrasystoles precipitated by the local application of a 5-per-cent solution of acetylcholine to the sinus node of the heart *in situ* Lead 2



FIG. 172.—From an experiment on a dog Auricular fibrillation precipitated by slight stretching of the auricular appendage after atropinization and subsequent topical application of acetylcholine to the sinus node of the heart *in situ*

observation that, in the spontaneously beating auricle of rabbits, paludrine inhibited the contractions which were then stimulated by acetylcholine: paludrine reversed the usually depressant effect of this compound (Burn and Vane). The same change could be demonstrated, without paludrine, by allowing the auricles to beat until they were exhausted and contractions ceased after twenty-four to thirty-six hours; at this stage addition of acetylcholine caused contractions to occur again and further addition of the substance strengthened them (Bulbring and Burn). This was interpreted as indicating that contractions can only occur as long as the tissue is capable of synthesizing acetylcholine This view was strongly supported by the observation that acetylcholine added to powder prepared from *fresh* auricles *depressed* the synthesis, whereas added to the powder prepared from *exhausted* (stopped) auricles *augmented* it. There was thus a clear relationship between contraction and synthesis, and between change in activity and change in synthesis.

Burn (1950) put forward the suggestion that, just as in skeletal muscle acetylcholine is liberated by the nervous impulse, so in cardiac muscle the "mechanism for firing off the contraction is also acetylcholine, but instead of being liberated by a nervous impulse, it is synthesized and causes a contraction probably when a certain concentration is reached It is possible that the pacemaker controls the rate of beating by controlling the rate at which this concentration is reached". These considerations may well have a bearing on the mechanism underlying the ectopic impulse formation in parasystole.

In Nahum and Hoff's experiments on dogs, application to the area of the sinus node of acetyl-beta-methylcholine caused auricular fibrillation in some instances and did invariably so if, in addition, the auricles were stimulated mechanically Scherf and Chick, *investigating also in dogs the effect of acetylcholine* applied topically to the auricles and ventricles, made the following observations: Application of a 5-per-cent solution of acetylcholine to the area of the *sinus node* caused immediate auricular flutter or fibrillation (Fig. 170); this was invariably abolished by atropine. Acetylcholine applied in this way after atropinization no longer precipitated auricular fibrillation, but transient auricular tachycardia or auricular extrasystoles (*see* Fig. 171). But for about ten minutes after the application of acetylcholine the auricles were extremely irritable and the slightest mechanical stimulus provoked fibrillation. This is illustrated in Fig. 172, obtained in another experiment in which acetylcholine had been applied already three

times with the same result as that shown in Fig 170. Then atropine sulphate (0 1 mgm. per kg) was injected intravenously and acetylcholine applied locally once more to the sinus node. After the first few beats shown in Fig 172, the right auricular appendage was slightly stretched; this produced an immediate increase in rate of the prevailing sinus rhythm, quickly followed by auricular fibrillation.

Application of acetylcholine to the *ventricles* in the non-atropinized animal caused transient regular ectopic ventricular tachycardia and, on the whole, the response of the ventricles to the topical application of acetylcholine was similar to that of the auricles

As distinct from the topical application of acetylcholine, after its systemic application and complete atropinization mechanical or electrical stimuli applied to the ventricles precipitated temporary parasystolic arrhythmia whereby ectopic beats occurring in groups were also observed (Scherf, Chick, Scharf and Terranova) This has to be considered as another variety of a stimulating effect of this drug on ectopic impulse formation

The mechanism underlying such stimulating effect of acetylcholine on impulse formation is little understood Much work on this topic is in progress and any views on this subject can only be considered as provisional and largely hypothetical

Acetylcholine has been reported to shorten the chronaxie of the frog's ventricle (Fredericq) Hoffmann and collaborators demonstrated, by several pharmacological tests, the presence of an epinephrine-like substance in the perfusate of the isolated heart of several mammalian species after acetylcholine was liberated or nicotine injected into the heart. These authors consider the possibility that such release takes place in certain nervous structures of the heart and that such mechanism may have a bearing on " vagal escape " and on the accelerating effect of vagal stimulation after atropinization and after sympathectomy. McNamara and co-workers showed in the isolated heart of rabbits that the cardiovascular stimulation produced by acetylcholine is potentiated by calcium and attribute it to the release of a sympathomimetic substance, possibly epinephrine While these experiments demonstrate possible links between the stimulating action of acetylcholine and of adrenaline, it has to be borne in mind that these relationships are complex. topical application of epinephrine in a concentration of 1 . 1,000 and 1 : 10,000, following intravenous injection of 0 01 gramme of acetylcholine in the atropinized dog, did not produce ectopic rhythms (Scherf and Chick).

There is reason to assume that the suppression of ectopic rhythms by quinine and cocaine compounds may be due to their inhibitory effect on the liberation of acetylcholine (*see* Dawes 1946, Burn 1950, Feldberg 1950).

In sympathetic ganglia there seems also to exist some relationship between acetylcholine deficiency, failure of transmission of excitation, and spontaneous activity in the form of repetitive discharge. If the stellate ganglion was perfused with a solution deficient in calcium, it was observed that " the cells discharge spontaneously at a time when synaptic transmission is blocked In several experiments we have observed, during the early stages of low calcium, the development of repetitive after-discharge following each preganglionic volley " (Bronk *et al.* 1938) This was confirmed by Harvey and MacIntosh and attributed to failure of acetylcholine to appear in active concentration. While observations made on one kind of tissue cannot be applied to another without the greatest reserve, these observations are quoted to draw attention to the simultaneous presence of a state of blocked transmission of impulses and enhanced spontaneous impulse formation, in which acetylcholine deficiency seems to play a part and which may well have a bearing on the mechanism underlying parasystole (*see* chapters on " Pararrhythmias " and on " Mechanism ").

Clinical Observations

At one time, choline and related substances were used for the purpose of stopping attacks of paroxysmal tachycardia (Boden and Wankell, Starr, Morgan), but in view of the

unpleasant side effects this method of treatment is now seldom used. In man, too, this group of drugs may precipitate ectopic beats (Boden and Wankell, Schliephake, Segers *et al.*), and this accords well with the analogous experimental findings that choline and derivatives may cause, as well as abolish ectopic arrhythmias.

Recognition of the stimulating effect of acetylcholine on ectopic impulse formation is of clinical interest as it affords an understanding of certain observations often termed paradoxical They include, for example, the occurrence of ventricular and auricular beats and tachycardias during carotid sinus pressure, and of ectopic arrhythmias in other circumstances associated with vagal stimulation.

Appreciation of the dual mode of action of these substances is of clinical importance as they are widely used in various clinical conditions

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ATROPINE

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Experimental

Nobel and Rothberger found in dogs anaesthetized with chloroform that after the administration of atropine larger doses of epinephrine were necessary to elicit ectopic arrhythmias (*see also* sections on "Chloroform" and on "Epinephrine") Ventricular extrasystoles produced in dogs by aconitine were abolished by atropine (Scherf 1929, *see also* section on "Aconitine") It could be shown that this effect was not due to the increase in the sinus rate, as extrasystoles remained absent if the sinus rhythm was slowed by cooling the sinus node A transient increase in the number of extrasystoles before their disappearance was also observed occasionally In more pronounced disturbances of rhythm, caused by aconitine, atropine was without effect

Of interest is the observation that, after atropinization, topical application of aconitine crystals to the ventricles of the exposed heart of dogs does not lead to ventricular fibrillation, whereas without atropine ventricular fibrillation invariably occurs after a ventricular tachycardia This experience also suggests a direct action of atropine upon the myocardium since direct vagal effects cannot be assumed to exist in the ventricles

In this connexion an observation made by Winterberg as early as 1908 is of interest, namely, that the administration of atropine makes it impossible subsequently to elicit auricular fibrillation by faradic stimulation of the auricles

Auricular fibrillation caused in the dog by focal application of aconitine to the auricular surface of the heart *in situ* invariably disappeared after the intravenous injection of large doses of atropine (Scherf, 1949) This was attributed to lengthening of the refractory period of the auricle

Clinical Observations

The suppression of extrasystoles by atropine in man has repeatedly been reported (Robinson and Draper, Halsey; Danielopolu and Proca 1925; Marchal and Heim de Balsac) Sometimes large doses of atropine were given for the purpose, as much as 3·6 mgm (Michailoff and Soltermann)

Gold and Otto reported that in five patients with bigeminal heart action due to digitalis 4 mgm of atropine given hypodermically in a single dose reduced the number of extrasystoles which finally disappeared altogether

In a series of eleven cases, Bourne gave atropine subcutaneously (grain 1/50) In ten of these, the number of extrasystoles diminished after the injection while, at the same time, the heart rate became slower for about four minutes as the result of the initial vagal

stimulation by atropine This observation demonstrates that the reduction in the number of extrasystoles could not have been due to a shortening of diastole (*see* also chapter on " Nervous System ").

The importance of atropine in preventing arrhythmias during cyclopropane anaesthesia is stressed in a more recent paper by Rink, Helliwell and Hutton. It is based on observations in forty-two patients operated for the relief of congenital pulmonary stenosis. Most of them were children. Pre-medication consisted of a full basal narcosis with nembutal (½ grain per 14 lb. body weight), and atropine grain 1/100. Regarding the importance of atropine these authors wrote: " Cardiac irregularity has likewise not been frequent and has been easily mastered by a brief period of substituting ether. This relative immunity from bradycardia and irregularity we ascribe to the use of a full dose of atropine; in Blalock's own practice, where much smaller doses were given, both these phenomena caused concern and had frequently to be corrected by a further dose administered intravenously."

While the effect of atropine in suppressing or preventing extrasystoles is established, occasionally the reverse action was observed, namely, that the administration of atropine elicited extrasystoles (Luten, Scott, Fogelson) In Danielopolu's case (1914), concerning a patient with occasional auricular extrasystoles, atropine precipitated continuous bigeminy, due to auricular extrasystoles. Galli reported an observation in which an attack of paroxysmal tachycardia occurred after atropine had been given orally as well as intravenously. Danielopolu and Proca claimed that ocular pressure rarely precipitated extrasystoles unless atropine had previously been given

The validity of a test, suggested by Leconte, to distinguish between " functional " and " organic " extrasystoles by the effect upon the ectopic beats of atropine seems questionable.

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PAPAVERINE

Experimental

Rossler, investigating the effect of papaverine on the dog's heart (Starling preparation), found an increase in contractility. According to Elek and Katz, in larger doses this compound is a cardiac depressant These authors also found lengthening of the refractory period of auricles and ventricles and, after intravenous injections of doses varying between 92 and 845 mgm per kg, observed in dogs disturbances of conduction, multifocal ectopic beats and paroxysmal ventricular tachycardias In therapeutic doses papaverine raises the fibrillation threshold (Lindner and Katz, Wégria and Nickerson) The mortality of dogs after ligation of coronary branches was found to be reduced by over 50 per cent as the result of prior administration of papaverine (McEachern, Smith and Manning)

Clinical Observations

In an early clinical study on the therapeutic uses of papaverine Pal (1914) observed the disappearance of extrasystoles

More recently Katz and Elek reported that in twelve patients with numerous extrasystoles the intravenous injection of 0 06–0·1 gramme of papaverine reduced their number considerably, sometimes abolished them altogether When this drug was given by mouth, in doses of 0 1–0 2 gramme, four or five times daily, a definite reduction in the number of extrasystoles was observed, the efficacy of papaverine being comparable, in this respect, to that of 0 2 gramme of quinidine, given four or five times daily This effect, on extrasystoles, of papaverine was not confirmed by Laake.

The intravenous administration of larger doses of papaverine to patients with damaged hearts is by no means free from risk We saw two patients die suddenly a few minutes after two intravenous injections, each of 0 06 gramme, of papaverine had been given in quick succession It is too readily forgotten that the experimental observations, discussed above, were obtained on normal hearts whereas clinically the drug is usually given to patients whose heart is anything but normal

SUMMARY

The effect of papaverine in suppressing extrasystoles is a useful property of this drug which, however, should never be given with the sole purpose of abolishing extrasystoles

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AMYLNITRITE

Experimental

In experiments on dogs Halsey found that ectopic beats caused by digitalis or strophanthin disappeared for a short time after the inhalation of amylnitrite. In one experiment, however, in which digitalis failed to produce such arrhythmia, ectopic beats were precipitated by amylnitrite and persisted for 90 seconds

Clinical Observations

In subjects prone to extrasystoles at certain times, amylnitrite—in doses commonly used for the relief of anginal pain—is apt to elicit the arrhythmia This effect is so frequent that it can be employed as a diagnostic test in cases in which the patient gives a history suggestive of extrasystoles, but does not exhibit any premature beats on examination—an occurrence which is by no means rare (*see* section on " Incidence ") (Scherf). In such instances extrasystoles are usually observed a few minutes after the inhalation of amylnitrite, during the height of the drug effect they are not present since the tachycardia, which is an immediate, but transient effect of the inhalation, with its ensuing shortening of diastole prevents their occurrence. In this respect the action of amylnitrite is analogous to that of exercise The most likely mechanism underlying this effect of amylnitrite is the pronounced fall in blood pressure with its resultant changes in the tone of autonomic nerves.

In subjects in whom extrasystoles were present before the inhalation, their number is often increased (Bourne) and inhalation for 15–20 seconds may even cause short attacks of paroxysmal tachycardia (Scherf, Scherf and Weissberg)

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SODIUM

The importance of the inorganic constituents of the perfusion fluid for the rhythmicity of the heart has been appreciated since Ringer's classical investigation in 1880

Regarding the part played by sodium, while a general discussion of this subject is outside the scope of this book, brief references may be made to a few papers emphasizing its importance for stimulus formation in the heart.

More than fifty years ago Greene found in strips of the apex of the terrapin's ventricle that, upon its immersion into a hypertonic solution of NaCl, rhythmic contractions started after a very short latent period According to Kisch, sodium salts in higher concentrations applied to the sinus node of frogs' hearts have no influence upon impulse formation, but Andrus and Carter found that substituting a 2-per-cent. solution of NaCl for Ringer's solution precipitated ectopic beats Baetjer and McDonald analysed in greater detail the ... interaction with

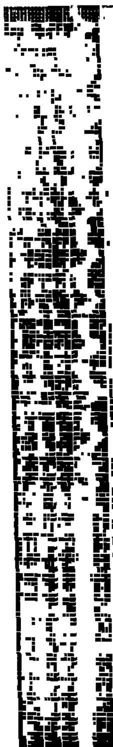


FIG 173.—From two different experiments on dogs *a* The beginning of ventricular tachycardia 12 seconds after brushing a 10-per-cent solution of NaCl on the conus area of the right ventricle *b* The two strips are continuous Auricular extrasystoles and short paroxysm of auricular tachycardia after application of a 5-per-cent solution of NaCl to the tail of the sinus node

by Piccione and Scherf. A 5-, 10- or 30-per-cent. solution was brushed on a small area of the surface of an auricle or ventricle, or 0·1 cc. of a 10-per-cent. solution was injected subepicardially By either method was it possible to elicit extrasystolic arrhythmias, but the latter produced the irregularities more constantly and more readily, and they occurred far more frequently in the ventricles than in the auricles. Such arrhythmias started within a few seconds of the interference and disappeared within a few minutes

Fig 173 illustrates such observations. Fig. 173a shows the beginning of a paroxysm of ventricular tachycardia which started twelve seconds after brushing a 10-per-cent. solution of NaCl on the conus area of the right ventricle. Such tachycardias were regular and came

either to the mechanical stimulation by the application or injection, or to the osmotic pressure of the hypertonic solution Fig. 173b, taken from another experiment, shows numerous auricular extrasystoles and a short paroxysm of auricular tachycardia following the application, to the tail of the sinus node, of a 5-per-cent. solution of NaCl In the last part of the tracing blocked auricular extrasystoles from another centre were recorded, one of which can be seen during the attack of tachycardia

By the same method auricular or ventricular bigeminy and trigeminy could be produced

An important feature of such arrhythmias is that the coupling of the extrasystoles was always constant in any given experiment This suggests that the ectopic beats originated in the same circumscribed focus, where they were precipitated by the preceding beat, that is, they were extrasystoles in the strict sense of the term. This view is supported by the observation that warming, by means of a thermode, of the site of application of the NaCl solution invariably increased the number and the rate of the extrasystoles, or caused them to occur in those instances in which injection alone had failed to elicit them (Scherf). This last observation warrants the conclusion that the site of application of the hypertonic solution was the site of the focus giving rise to the ectopic beats.

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POTASSIUM

Experimental

producing cardiac standstill (Blake 1839, Traube 1864, Guttmann 1866, Boehm 1877, Braun 1904), but at an early stage it was recognized that the resulting condition actually was ventricular fibrillation (Aubert and Dehn 1874). Subsequent investigations emphasized the complexity of the potassium effect on cardiac activity.

It was shown by Gross (1903) that the mode of action of potassium salts depended *inter alia* on whether they were applied to the isolated heart, or to the animal with the heart *in situ* in the former event it produced cardiac standstill, in the latter ventricular fibrillation The results of Hering's experiments, published in the same year, pointed in the same direction: he demonstrated that ventricular fibrillation, induced in the isolated mammalian heart by various agents, was *abolished* by the administration of potassium; after its removal rhythmic contraction set in again These findings were confirmed by Mathison and by Wiggers (1930a) In a later series of experiments Hering (1915) emphasized the differences between the isolated heart and that *in situ* regarding its reaction to potassium intravenous injection of 4 cc. of a 1-per-cent solution of KCl *precipitated* ventricular tachycardia in rabbits, and ventricular fibrillation in dogs.

An inhibitory action upon ectopic rhythms of potassium salts was found by McCord, Hofmann; Kolm and Pick, and, regarding isolated Purkinje fibres, by Ishihara and Pick.

It was thus demonstrated that the systemic application of potassium salts may precipitate, as well as inhibit, ectopic arrhythmias and that one of the factors responsible for this seemingly contradictory effect of the salts was whether they had been applied to the isolated heart or that *in situ* Others were the concomitant exhibition of other drugs, and dosage.

Regarding the former of these, it was established by Scherf, and confirmed by Hueber, that in dogs treated with such small doses of aconitine that the electrocardiogram remained unchanged, the intravenous injection of 0 005–0 05 gramme KCl invariably elicited ventricular extrasystoles with accurate coupling, and ventricular tachycardia Such arrhythmias disappeared within a few minutes and could be brought out again by a renewed injection of KCl. In this connexion it is noteworthy that in Hering's experiments of 1915, quoted above, prior to the administration of KCl, delphinine had been employed which, according to unpublished observations (Scherf), exerts upon ectopic impulse formation an effect similar to that of aconitine

Dosage was established as a further important factor to account for the paralysing or stimulating effect, respectively, upon ectopic impulse formation of potassium salts

Wiggers (1930a), as already mentioned, reported the abolition by KCl of ventricular fibrillation caused in various ways In such experiments on cats and dogs he injected 50 mgm (1 cc of a 5-per-cent solution) per kg into the ventricular cavities In further investigations (Wiggers, 1930b) he established that smaller doses—for instance, the fast intravenous injection of 30–100 mgm—had in dogs the reverse effect, namely, elicited ventricular fibrillation Wiggers explained the last finding by the assumption that such smaller doses produce disturbances of conduction, causing the setting up of islets of refractory tissue and resulting in circus movement of the excitation wave, without inhibition of stimulus formation If, on the other hand, doses of not less than 50 mgm per kg are injected intravenously the excitability of the whole heart is diminished, impulse formation as well as conduction being affected, and the result is cardiac standstill If it is desired to abolish ventricular fibrillation the potassium salt should preferably be injected simultaneously into both ventricles

Ventricular fibrillation caused by potassium shows certain characteristic features differentiating it from ventricular fibrillation caused by other means (W[illegible]

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caused ventricular fibrillation within one or two minutes On the other hand, that of 30–50

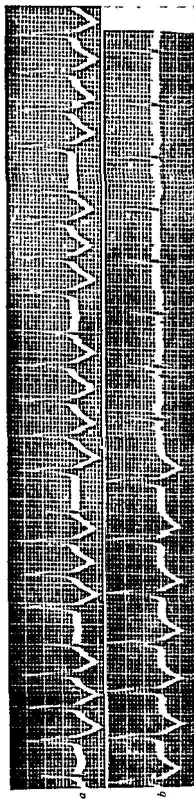


Fig 174.—From an experiment on a dog a Extrasystolic arrhythmia elicited by the topical application of sodium chloride to the conus of the right ventricle b Suppression of the ectopic rhythm by the topical application of potassium chloride to the same area For further explanation, see text

cc. of a 1-per-cent. solution, given at a rate of 1–2 cc. per minute, was followed in rabbits and cats by a diminished rate of stimulus formation, disturbances of conduction and cardiac standstill, without any ectopic impulse formation being observed. The ventricular fibrillation caused by the rapid injection was attributed to disturbances of conduction occurring before depression of impulse formation had become manifest—a conception very similar to that of Wiggers, discussed earlier

Chamberlain, Scudder and Zwemer found in cats that slow intravenous injection of potassium salts was followed first by ventricular ectopic beats, then by ventricular paroxysmal tachycardia and, finally, by ventricular fibrillation The various arrhythmias corresponded to different blood levels of potassium

As distinct from the *systemic* administration of potassium salts, discussed so far, their *topical* application has, on the whole, only a depressant effect.

According to Kisch topical application of potassium salts to the sinus node of the frog's heart causes increase in the rate of impulse formation; this was found to be more pronounced if previous manipulations had resulted in a slowing of rate (Kisch, 1926a)

With a similar method Hofmann found in the mammalian heart that topical application of potassium chloride (1 per cent) caused inhibition of stimulus formation in the sinus node.

In the dog, topical application of a 5-per-cent solution of KCl to the area of the sinus node, or to different areas of the ventricular surface, never produced premature or ectopic beats (Boyd and Scherf). On the contrary, if such arrhythmias had been produced by means of sodium or barium applied topically by the same technique, subsequent application of KCl to the same area abolished them immediately (Piccione and Scherf). This is illustrated in Fig 174

Fig 174a shows series of three or more extrasystoles occurring in succession which had been elicited by brushing a 10-per-cent. solution of NaCl on to a small area (4 mm diameter) of the conus of the right ventricle. The first extrasystole of such series was accurately coupled to the preceding beat. Subsequent application of a 5-per-cent. solution of KCl to the same area

first slowed the ectopic rhythm and then abolished the extrasystoles (Fig 174b). Similar results were obtained in regard to ectopic beats precipitated by the topical application of digitalis (Scherf, unpublished observations). If by the sub-epicardial injection of 0 05 cc of a 0 05-per-cent solution of aconitine into the area of the sinus node auricular flutter or auricular fibrillation had been elicited, injection into the same area of 0 05 cc. of a 1-per-cent. solution of KCl restored sinus rhythm immediately (Scherf and Terranova).

Clinical Observations

Clinical observations are in accordance with those made experimentally that potassium may abolish as well as precipitate ectopic arrhythmias Thus, extrasystolic arrhythmias [illegible]

(Eliel *et al*) and ventricular bigeminy with low serum potassium during p-amino-salicylic acid treatment (Cayley) On the other hand, ectopic arrhythmias have been reported in patients with hyperkalaemia (Somerville; Levine, Merrill and Somerville) The complex [illegible]

In fifty-eight patients with auricular or ventricular extrasystoles Sampson and Anderson studied the effect, upon the arrhythmia, of various potassium salts, they included bromide, iodide, acetate, chloride and citrate. In twenty-nine cases a definite reduction in the number of extrasystoles was observed, in ten the results were doubtful and in sixteen no effect was seen Three patients responded by an increase in the number of extrasystoles, one of whom developed an attack of ventricular paroxysmal tachycardia The effective dose varied between 1 and 16 grammes a day in different individuals It took between forty and ninety minutes for a single oral dose to produce an effect which lasted for between three and eight hours In older patients, and those with structural heart disease, the smaller doses proved effective In those cases in which no effect was observed, inadequate dosage or impaired absorption could be excluded as high potassium levels in the serum were found Untoward effects consisted in abdominal cramps and diarrhoea; of the various salts, the acetate caused the least gastro-intestinal disturbance [illegible]

Similar beneficial effects in the treatment of extrasystoles by potassium salts were seen [illegible]

Allott, Castleden and Walker)

[illegible]

to a diminished amount of potassium in the cells.

SUMMARY

In experimental work it has been established that potassium salts may abolish, as well as precipitate, ectopic arrhythmias The factors responsible for the kind of action are not fully understood The effect was found to depend, *inter alia*, on whether the salts were applied to the isolated heart or to the animal with the heart *in situ*, on the concomitant employment of other drugs, the speed of injection and on the dosage used. Topical application of potassium salts, by means of brushing KCl solution on circumscribed areas of the exposed heart, or by sub-epicardial injection, have almost exclusively a depressant effect on such arrhythmias

Clinical observations have shown that ectopic arrhythmias are found in association with hypo- as well as hyper-potassemia Potassium salts have a limited value in the treatment of extrasystoles The effective dose varies greatly in different individuals. Their effect is not constant and in some cases they may precipitate ectopic arrhythmias. Renal disease is a contra-indication against the use of potassium salts which, in any case, are much inferior to other drugs (for example quinidine) and which should only be given under medical supervision *See also* section on " Treatment ".

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CALCIUM

Whereas the importance of the calcium ion for maintaining *normal* impulse formation has been firmly established since the classical work of Ringer, Lingle, Howell a o., its effect upon *ectopic* impulse formation is far from clear Experimental as well as clinical observations are conflicting and much seems to depend on the species studied, the dose employed and other drugs given in conjunction with it

Experimental

Stimulation as well as inhibition of ectopic impulse formation has repeatedly been reported, a few examples may be quoted

On the isolated ventricle of the frog's heart Sakai found that small doses of calcium increased automatic rhythm whereas large ones had the reverse effect

Direct application, to the sinus node of the frog's heart, of calcium chloride in the lowest effective concentrations (m/100–m/75 $CaCl_2$) was found to inhibit normal impulse formation, higher concentrations (m/5 $CaCl_2$) increased it whereas still higher ones again resulted in inhibition If different concentrations of calcium chloride were topically applied to the ventricles the ectopic centres were affected in the same way here, too, small and large doses inhibited, whereas medium doses enhanced impulse formation The latter effect manifested itself also by multiple responses of the heart to one mechanical stimulus Different results obtained by other investigators were explained as due to the use of different preparations and to differences in prior experimental interferences ("Vorgeschichte des Praparates") (Kisch) In the isolated sinus of the terrapin's heart focal application of calcium inhibited automaticity (Baetjer and McDonald)

In the mammalian heart the effect of calcium was found qualitatively similar to that of barium (in rabbits Frommel; in dogs Rothberger and Winterberg, Egmond), but larger doses of calcium were necessary to produce the same effects In Rothberger and Winterberg's experiments on dogs it was found that, after the intravenous injection of 0 05 gramme

of calcium chloride, simultaneous faradic stimulation of vagus and cardiac sympathetic was *followed by ectopic ventricular beats. With larger doses of calcium these occurred after* stimulation of the sympathetic alone, and still larger doses (0·1–0·2 gramme) precipitated ventricular tachycardias without any stimulation of cardiac nerves (These doses should be compared with those of barium employed in analogous experiments; *see* section on " Barium " and chapter on " Nervous System ", pp. 347 and 254.) The ectopic rhythms produced by calcium resembled those following administration of barium also in that the ectopic beats had varying coupling and varying shapes in the electrocardiogram; bigeminal rhythms with accurately coupled extrasystoles were not observed. Regarding the importance of this distinction, *see* chapter on " Mechanism ".

The intravenous injection of 1–2 cc. of a 10-per-cent. solution of calcium chloride in dogs caused sinus bradycardia, auricular fibrillation and disturbances of A-V conduction (Hoff *et al*, 1939) If larger doses were injected and concentrations of calcium in the serum of 30–65 mgm in 100 cc. attained, ectopic beats, bigeminal rhythm, ventricular tachycardia and ventricular fibrillation ensued. Such abnormal rhythms could sometimes be suppressed by sodium amytal (Hoff and Nahum, 1937)

Scherf, on the other hand, observed that extrasystoles produced by aconitine were suppressed by calcium given intravenously It should be remembered, however, that extrasystoles produced by aconitine respond in a paradoxical way to the stimulation of the cardiac sympathetic and of the vagus, respectively (*see* chapter on " Nervous System," p 255)

Studies on the effect of calcium on the rhythmicity of Purkinje fibres emphasized the importance of the concentration of the element: Ishihara and Pick reported an increase in rate of the automatic rhythm whereas, according to Goldenberg and Rothberger, large doses of calcium invariably inhibited automatic rhythms. In the isolated mammalian left auricle addition of 1–3 cc of a 5-per-cent. solution of calcium chloride to the Soejima solution abolished spontaneous contractions (Rothberger and Sachs).

Focal application of calcium chloride to the epicardium of the dog's heart only occasionally caused isolated ectopic beats; this is in marked contrast to the profound effect of sodium or barium (*q v*) (Piccione and Scherf)

[illegible]

lished automatic rhythms which had been abolished by strophanthin.

Clinical Observations

The experimental findings that calcium may abolish as well as elicit ectopic arrhythmias and even inhibit normal stimulus formation is duplicated by clinical observations in which [illegible]

and paroxysmal tachycardias (Petzetakis, Wolffe and Bellet; Clarke) while the same dosage precipitated such arrhythmias in others. Berliner, who used 10 cc. of a 20-per-cent. solution of calcium gluconate in twenty-six patients who had not received digitalis previously, saw ventricular extrasystoles appear in two patients. Following intravenous administration of 40 grains of calcium chloride in a 2-per-cent. solution Clarke observed ectopic beats and ventricular tachycardias in a patient without any evidence of heart disease and without premedication with digitalis Concerning the effect on normal impulse formation, Berliner [illegible]

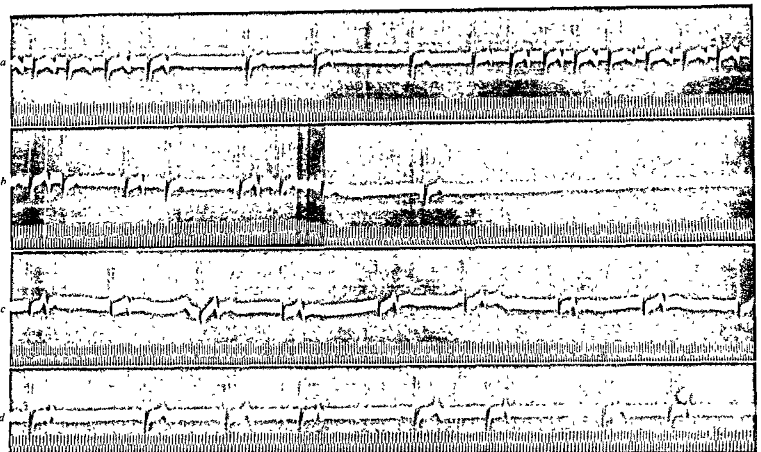


FIG 175.—All records lead 2 Before and after the intravenous injection of 10 cc of a 10-per-cent solution of calcium chloride
For explanation, see text

Two instances of death, following the intravenous injection of calcium have been reported by Bower and Mengle in patients who had been given digitalis previously. One of these was a thirty-two-year-old woman without organic heart disease who had received 15 cc. of digalen within six days Two minutes after the intravenous injection of 10 cc of a 10-per-cent solution of calcium gluconate no heart sounds were heard and the patient died. The other patient was a fifty-five-year-old man admitted for a fracture of the femur. Eight and one-half cc. of digalen had been given within twenty hours and the subsequent injection of 10 cc. of a 10-per-cent. solution of calcium gluconate caused death within two minutes According to Bower and Mengle the effect, upon impulse formation, of calcium gluconate resembles that of calcium chloride.

Such observations demonstrate that the intravenous use of calcium even in patients without organic heart disease is by no means free from risk. This applies equally to cases with or without prior or simultaneous administration of digitalis

That even in subjects without evidence of structural heart disease the intravenous administration of calcium may be followed by most unpleasant reactions is illustrated by observations on a twenty-three-year-old man who, otherwise healthy, suffered from numerous short attacks of auricular paroxysmal tachycardia, which were separated by a few beats of normal sinus rhythm, that is, " Extrasystolie à paroxysmes tachycardiques " (*q.v.*) The frightening sequence of events which followed an intravenous injection of 10 cc. of a 10-per-cent solution of calcium chloride is illustrated in Fig 175

Fig 175a, recorded before the injection, shows the end of one, and the beginning of another of such attacks The ectopic beats have peaked inverted P waves. Fig 175b, obtained about forty seconds after the injection, shows auricular bigeminy with gradually lengthening P-R intervals of the extrasystoles from 0·22 to 0 36 second, followed by complete cardiac standstill lasting for more than one-and-a-half minutes which was associated with loss of consciousness. Following several blows to the precordium cardiac contractions started again At first, the rhythm (*see* Fig. 175c) was a slow A-V rhythm, either with preceding activation of the ventricles and disturbances of intra-auricular conduction as manifested by the differences in shape of the P waves, or with blocked auricular extrasystoles Subsequently (*see* Fig 175d), a slow sinus rhythm re-established itself, with blocked auricular extrasystoles, having a shape different from those reproduced in Fig 175a Fortunately the patient recovered completely from this dangerous and frightening incident.

SUMMARY

Experimental as well as clinical observations have shown that calcium salts may precipitate as well as abolish ectopic arrhythmias The kind of action seems to depend on the *species studied, on the dose employed, and on the simultaneous administration* or otherwise of other drugs The intravenous use of calcium salts is not free from risk, irrespective of whether they are given alone or in conjunction with digitalis. A potentiating action of calcium regarding digitalis cannot be considered as established

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BARIUM AND STRONTIUM

Barium

While in clinical practice the importance of absorbed barium salts is confined to the occasional—and fortunately rare—cases of accidental intoxication by soluble barium salts, they have played a conspicuous rôle in the physiological studies of ectopic cardiac arrhythmias

Experimental

In an extensive series of investigations, already referred to in the chapter on the "Nervous System", Rothberger and Winterberg first employed in 1911 barium in the form of its chloride to study electrocardiographically the arrhythmias occurring in the dog's heart *in situ* These authors found that ectopic beats, originating in a ventricle as a result of the simultaneous faradic stimulation of the (preferably right) vagus and sympathetic nerves, occurred more readily if the animal had previously been given small doses of barium chloride (0 005–0 01 gramme) intravenously With larger doses (0 025–0 05 gramme) such arrhythmias were observed after stimulation of the left accelerans without simultaneous vagal stimulation Still larger doses (0 05–0·1 gramme) precipitated ectopic arrhythmias without any stimulation of cardiac nerves A similar sensitizing action of barium was observed regarding epinephrine (*q v*)

These effects of barium, namely, either to predispose the heart in certain experimental conditions to develop, or actually to cause, ectopic arrhythmias have subsequently been

confirmed and studied in various ways. In experiments on the perfused heart of dogs, in which complete A-V block had been produced, Egmond found this element to cause ventricular ectopic beats and tachycardias. Also in experiments on dogs Scherf (1926, 1927) demonstrated that, after injection of such small doses of barium that the electrocardiogram remained unchanged, mechanical or electrical stimulation of a ventricle caused series of ectopic beats, and local thermal stimulation, by means of a thermode, ventricular tachycardia, such arrhythmias originating at the site of stimulation.

Ventricular tachycardias elicited by large doses of barium can be abolished by the inhalation of a mixture of 20 per cent CO_2 and 80 per cent. O_2, whereas quinidine terminated such arrhythmias in only four out of ten experiments (Friedberg and Levinson)

The stimulating effect of barium, upon impulse formation, was also found in isolated Purkinje fibres of the dog's heart (Ishihara and Pick), and various types of arrhythmias, sometimes resembling bigeminal rhythm, were observed by Wachstein on strands of Purkinje fibres On isolated muscle bundles of the frog's heart barium chloride constantly initiated automatic activity, the threshold concentration being $0{\cdot}3 \times 10^{-7}$ mol /ml (Deutsch and Lundin)

An important feature of the ectopic arrhythmias caused by barium, which were encountered in the investigations discussed so far, is that the ectopic beats showed varying shapes in the electrocardiogram and were not accurately coupled to the preceding beat If three or more ectopic beats occurred in succession they did so in an irregular sequence. In dogs, extrasystoles with accurate coupling, so frequently observed in clinical practice, could not be precipitated with any constancy by the systemic administration of barium salts. In rabbits, on the other hand, anaesthetized with morphia and sensitized with small doses of barium, Schott observed long series of bigeminal rhythm, due to ventricular extrasystoles with accurate coupling, as a result of clamping both carotid arteries (*see* chapter on " Nervous System ")

In dogs, such arrhythmias could be elicited by the *focal* application of barium chloride (Piccione and Scherf). This was achieved, either by brushing a 2–5-per-cent. solution on a small area (2–3 mm diameter) of the epicardium, or by the sub-epicardial injection of 0·05–0·1 cc of a 1-per-cent solution In this way bigeminal rhythm with constant coupling of the extrasystoles, trigeminy and various other ectopic arrhythmias could be precipitated. Figs 176 and 177 illustrate some of them

The tracing reproduced in Fig. 176a was recorded after a 1-per-cent. solution of barium chloride was brushed on a small area of the conus of the right ventricle. Extrasystoles originating at the site of application of the salt were observed after a latent period of six minutes The figure shows bigeminal rhythm, one ventricular extrasystole occurring after each sinus beat The length of the coupling alternates between 0·44 and 0·46 second As every second extrasystole occurred very late in diastole, at a time when most of the P wave of the next sinus beat was already inscribed, these late extrasystoles show in the record the shape of combination beats (namely, a combination between the undistorted shape of the extrasystoles as exemplified in the complexes of the series of the earlier extrasystoles, and that of the sinus beats), the ventricles being activated at such times partly by the ectopic, and partly by the sinus impulse.

In the experiment from which Fig 176b was obtained, 0·05 cc. of a 1-per-cent. solution of barium chloride had been injected sub-epicardially near the apex of the left ventricle After an interval of eleven minutes series of five to six extrasystoles in succession were recorded after each sinus beat, the first extrasystole of each series showing constant coupling, and the rhythm of the short paroxysms being fairly regular. Such arrhythmias were usually transient and rarely lasted more than one minute. At other occasions ventricular tachycardia with irregular rhythm was observed (Fig 177).

FIG 176 — From two different experim... of the conus of the right ventr... 1 per cent solution of barium chloride to the conus of barium chloride near the apex of the left ve... tial injection of 0 05 cc of a 1 per cent solution of barium solution ..., see text.

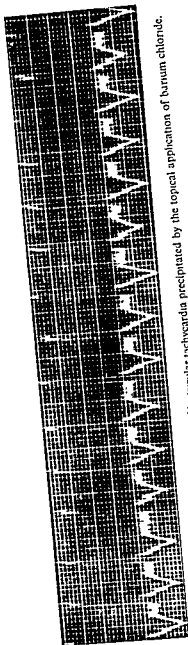


FIG 177 —From an experiment on a dog Ventricular tachycardia precipitated by the topical application of barium chloride.

It is remarkable that ventricular tachycardias caused by barium salts, whether administered intravenously or applied topically, always showed such irregularities in the ectopic beats and often also different shapes of the ventricular complexes. The significance of a sharp distinction between ectopic beats with accurate coupling (and constant shape) in the electrocardiogram, and those with varying coupling (and varying shapes) is discussed in the chapter on "Mechanism"

Clinical Observations

Cases of poisoning by soluble barium salts are on record in which irregular heart action was observed which can be attributed to ectopic arrhythmias Such incidents have been reported in connexion with radiological investigations (Krause and Käding, Hirvonen), or due to contamination of flour with barium carbonate intended as rat poison (Morton).

Because of the narrow margin between therapeutic and toxic doses the use of barium chloride, recommended in doses of 20–30 mgm three to four times a day by Cohn and Levine for the treatment of Stokes-Adams attacks in complete A-V block with slow ventricular rate, should be discouraged Untoward effects have been described by McMillan and Wolferth, and by Mahaim Ephedrine is far preferable in such cases On no account should epinephrine be given in combination with barium

Strontium

On isolated muscle fibres of the frog's heart Deutsch and Lundin found that addition of strontium salts to the nutrient solution increased the automaticity in a way similar to barium, but in order to produce a threshold effect fifty times as much strontium was required.

In experiments on dogs the intravenous injection of 10–15 cc. of a 10-per-cent. solution of strontium chloride did not cause ectopic beats (Rothberger and Winterberg) These authors considered the possibility that larger doses may have a similar effect as barium salts, since previous experiments on cats had shown that "several cc" of a 20-per-cent. solution of strontium caused arrhythmias (no electrocardiograms were taken).

SUMMARY

In experimental work barium chloride has played an important part in the investigation of ectopic arrhythmias. Its systemic application, either alone in larger doses, or in smaller doses combined with other experimental interferences, precipitates with rare exceptions ectopic beats with varying coupling and varying shapes in the electrocardiogram, or ectopic ventricular tachycardias. Topical application of this compound to the exposed surface of the heart, on the other hand, elicits extrasystolic arrhythmias with constant coupling of the extrasystoles, apart from various other ectopic arrhythmias The relevant literature on these investigations is reviewed and some aspects are illustrated by personal observations The clinical use of barium chloride in the treatment of Stokes-Adams' attacks in complete A-V block is discouraged

Brief reference is made to the very scanty literature on the effect of strontium salts regarding ectopic arrhythmias

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MAGNESIUM

The general effect of the magnesium ion on the heart is that of a cardiac depressant; for a short review of the relevant literature *see* Kisch (p 750)

Experimental

In early studies on ectopic arrhythmias it was noted that magnesium salts failed to have any stimulating effect on ectopic impulse formation (Rothberger and Winterberg, Abderhalden and Gellhorn) The effect, upon such arrhythmias, of magnesium salts did not attract much interest when it was found that their intravenous administration abolished arrhythmias which occurred in cattle as a result of calcium injections given for the treatment of "milk fever" and "grass tetany" (Seekles, Sjollema and van der Kaay)

The use of magnesium salts in the treatment of ectopic arrhythmias in man is largely based on the report of Zwillinger in 1935 who found that magnesium sulphate abolished in man ventricular extrasystoles produced by digitalis Subsequently Rothberger and Zwil- [illegible] these authors recommend the use of magnesium gluconate as it results in a smaller drop in blood pressure than other magnesium salts Szekely and Wynne produced ectopic ventricular arrhythmias in cats by means of digitalis and strophanthin and found that magnesium sulphate (0 5–3 5 cc of a 20-per-cent solution, given intravenously) abolished ventricular extrasystoles in all four instances of bigeminy and restored sinus rhythm in three out of eight instances of ventricular tachycardia

More recently, Pines, Sanabria and Arriens observed in dogs a protective action of magnesium sulphate against ventricular fibrillation resulting from mercurial diuretics and recommended the incorporation of small quantities of this salt (0 5 cc of a 20-per-cent solution) into the solution of the mercurial diuretic. (While this observation is of considerable physiological and pharmacological interest we should like to emphasize that, in our opinion, clinically mercurial diuretics should only be given intramuscularly)

Like so many compounds, magnesium salts may in certain circumstances have the opposite effect, namely, precipitate ectopic arrhythmias (Smith, Winkler and Hoff 1939, Miller and van Dellen)

Clinical Observations

As already mentioned, in 1935 Zwillinger recommended the intravenous administration of magnesium sulphate for the treatment of extrasystoles and paroxysmal auricular tachycardia. Ten to twenty cc. of a 15-per-cent solution, or 10 cc. of a 30-per-cent. solution were found to abolish digitalis extrasystoles (Zwillinger, Bloch and Pick) On the basis of experimental observations Smith, Winkler and Hoff (1939, 1942) expressed doubts whether the salt in the recommended doses could have much effect on cardiac rhythm, but Boyd and Scherf confirmed the efficacy in terminating attacks of paroxysmal auricular tachycardia: in eight instances the slow intravenous injection of 15–20 cc. of a 20-per-cent. solution *stopped the attack in every case within a few seconds without any untoward effect.* Favourable results in paroxysmal auricular tachycardia were also reported by Szekely, and in ventricular ectopic rhythms due to digitalis by Szekely and Wynne. In ectopic arrhythmias caused by digitalis, injections of magnesium may be life-saving, but should not be repeated at short intervals because of the depressant effect of the salt upon the myocardium

In clinical observations, too, the opposite effect of magnesium sulphate was occasionally found (Boyd and Scherf). Sometimes, in cases of paroxysmal tachycardia, ventricular extrasystoles temporarily occurred immediately after the injection In patients with ventricular extrasystoles a transient increase in their frequency and sites of origin was often observed (Enselberg *et al*). Such clinical findings accord well with similar experimental ones, referred to above

SUMMARY

The rather scanty literature on experimental work on the effect of magnesium salts on ectopic arrhythmias is reviewed Regarding the clinical application, it is concluded that the intravenous administration of magnesium sulphate has a place in the treatment of paroxysmal *auricular tachycardia.*

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MERCURIAL COMPOUNDS

Experimental

In experimental work organic mercurial compounds have been found to produce ventricular premature beats, ventricular tachycardia and finally ventricular fibrillation (Salant, Jackson, McCrea and Meek, Barker *et al*) The doses employed in such investigations were, however, considerably higher than those given in clinical practice According to Pines, Sanabria and Arriens this action of mercurial compounds can be prevented by magnesium sulphate (*q v*)

Clinical Observations

With the introduction of mercurial diuretics into clinical practice the effect upon cardiac rhythm of such compounds became of great clinical importance That the intravenous injection of a mercurial diuretic may quickly be followed by sudden death has been known since Redlich's observation in 1925, concerning Novasurol More recently, such fatal accidents have been reported on several occasions and while in some cases they may have been due to an allergic reaction of the patient, in others ectopic arrhythmias were responsible Ventricular extrasystoles and ventricular tachycardia were observed by Chastain and Mackie, Volini, Levitt and Martin, Ben-Asher In a recent investigation by Wolff and [illegible] mal tachycardia.

Occasional premature contractions were found in three out of a hundred patients who had received injections of Thiomerin, a more recent mercurial diuretic (Herrmann *et al*)

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MISCELLANEOUS DRUGS

This section is devoted to brief notes on some compounds which have or may acquire some experimental or clinical interest in connexion with ectopic arrhythmias, but which do not warrant a more detailed discussion.

Ergotamine. With the recent discovery of the di-hydrated alkaloids of ergot their effect on ectopic arrhythmias was studied This seemed promising in view of the part played by the sympathetic in the precipitation of such arrhythmias and the sympatholytic effect of ergot alkaloids generally These comparatively recent studies are, at present, still very much in the beginning

Bennett, Dhuner and Orth found in dogs and monkeys that dihydro-ergocornine (DHO-180) seemed more effective than dihydro-ergotamine (DHE-45) in preventing ectopic arrhythmias induced by cyclopropane and epinephrine A clinical trial of such compounds on twenty-three patients was " far from conclusive ".

Rothlin and Cerletti reported that in dogs the pre-fibrillary ectopic arrhythmias due to chloroform-adrenaline could mostly be prevented by the intravenous injection of Hydergin (0·1 mgm. per kilo on an average) Hydergin consists of equal parts of the three alkaloids dihydroergocornine, dihydroergocristine and dihydroergokryptine and is also known as CCK 179 Further studies by these workers are announced about the extent of such protection against arrhythmias produced in various ways and about the mode of action of such protection

Methyl fluoroacetate, which was introduced as a rodenticide, caused ventricular fibrillation in monkeys, rabbits, goats and horses, but not in dogs and guinea pigs (Chenoweth and Gilman). These studies emphasize the pronounced differences in the reaction to this compound of various species.

Emetine has been reported to cause ectopic beats both experimentally (Boyd and Scherf) and clinically (Baer; Hardgrove and Smith; Klatskin and Friedman) In clinical practice ectopic arrhythmias play only a very small part compared with other electrocardiographic and toxic manifestations of this compound.

During intravenous administration of **histamine** to twenty-five patients ventricular extrasystoles were seen in four instances when the injection was given rather quickly (Peters and Horton)

Ventricular extrasystoles were also observed as a result of the administration of low **fatty acids** (Hall and Waldman)

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CHAPTER IX

SOME MAINLY PHYSIOLOGICAL ASPECTS OF EXTRASYSTOLES AND OF ECTOPIC BEATS GENERALLY

DYNAMICS OF CONTRACTION AND REFRACTORY PERIOD OF EXTRASYSTOLES AND POST-EXTRASYSTOLIC BEATS

Extrasystoles and Ectopic Beats Generally

The force of an artificially induced cardiac contraction is independent of the intensity of the stimulus: the all-or-none law. Bowditch's description, in 1871, of his fundamental discovery of this law, in the apex of the frog's heart, is of such admirable lucidity that it deserves to be quoted:

"An induction current of the smallest intensity which yields a cardiac contraction does not produce the smallest possible contraction, nor does the force of the latter increase to a [illegible] In our preparation the induc- [illegible] he former, it produces at once [illegible] licit at the given moment It follows that variations in strength of contractions of the cardiac apex are due to variations in the condition of its muscular fibres. It seems hardly necessary to emphasize the great practical importance of this sentence." (P 174, our translation)

This law was found to be valid for the mammalian heart by McWilliam (1888) and is now universally accepted It is true that [illegible] however, by Bornstein (1906b) and by Koch, that such observations can be reconciled with the all-or-none law if the velocity of conduction of the impulse is taken into consideration A stronger stimulus directly affects a greater number of fibres In normal conditions, the velocity of conduction is so great that the number of fibres directly stimulated is immaterial, as far as the resulting force of contraction is concerned. In hypodynamic hearts, on the other hand, conduction may be retarded to such an extent that considerable differences in the period of latency and in speed of contraction exist between the various areas, so that a direct stimulation of a larger number of fibres produces a stronger contraction

Kleinknecht showed manometrically on the hearts *in situ* of frogs cooled to a rectal temperature of —3 C that extracontractions, precipitated by induction shocks just before the next normal contraction was due (that is very late in diastole), yielded higher intraventricular pressures than normal beats, and that a stronger stimulus produced a greater increase in pressure even if it occurred a little earlier in diastole and thus at a moment when recovery was less complete He explained this apparent exception from the all-or-none law by the assumption that, owing to the pronounced cooling, conduction of the impulse of normal beats was slowed and thereby lead to a smaller increase in intra-ventricular pressure than that produced by the artificial beats in which many fibres were simultaneously stimulated Again, the reduced velocity of conduction is held to account for the apparent anomalies

The all-or-none law does not mean that the force of contraction of artificially produced

beats is constant for any given preparation. On the contrary, Bowditch, in his paper of 1871 already quoted, pointed out that: " Cardiac muscle possesses the notable property that its susceptibility for stimuli is altered by the contractions which it has performed, that is to say after a longer series of contractions a weaker stimulus very often is effective in producing a regular sequence of pulses than had been the case before." (P. 151, our translation) Bowditch also found that, if the apex of the frog's heart is stimulated after a longer interval, the contractions increase in height, at first steeply and subsequently more gradually, until a maximum is reached Woodworth confirmed this observation of the " staircase " phenomenon for the mammalian heart (spontaneously beating apex of the dog's heart). It is due to a temporary increase, by the contraction, of the contractility of the heart in the event of a subsequent stimulation, provided the stimuli follow one another at sufficiently short intervals, and is probably related to, or a manifestation of, the supernormal phase of recovery (*see* chapter on " Mechanism "). During the interval after a contraction the heart regains its excitability, being refractory during most of systole The length of the optimum interval between two successive stimuli for yielding maximum contractions depends on two opposite forces the stimulating effect of a rapid succession of contractions, and the recuperative effect of a long pause Woodworth showed that, in this respect, a difference exists between the frog's and the dog's heart in the former the optimum interval between two successive stimuli is four to five seconds whereas in the latter it is about one second He demonstrated that the strongest possible contraction occurred if two or more contractions were elicited in rapid succession and then the apex was stimulated after a considerable interval, conversely, the smallest contractions were observed if the apex was at first stimulated at a slower rate and the last of such stimuli was followed by one at the briefest possible interval While Woodworth attributed these observations to the effect, upon contractility, of contractions following one another in rapid or slow succession, the emphasis to-day is more on the supernormal phase of recovery and the varying duration of the refractory period as the main factors.

The refractory period is one of the important factors which, by affecting the condition of the heart muscle at the moment of a subsequent contraction, determine the strength of extra-contractions The fact that, during most of systole, the heart muscle is in an absolute refractory period which is followed by a stage of gradually increasing excitability, termed relative refractory period, is too well known to merit any detailed discussion. In general the extracontraction will therefore be the weaker the earlier in diastole it occurs. This has [illegible]

[illegible]

limits, an extracontraction can be elicited the earlier in diastole the stronger the extra-stimulus is—which is only another way of describing the relative refractory phase

A similar curve of the recovery of excitability is obtained if the duration of extrastimuli of constant intensity is varied Using condenser discharges as test stimuli, von Werz established that the longer the interval after the preceding excitation the shorter a test stimulus can be to elicit a contraction.

The refractory phase decreases with increasing rates and that of an extrasystole is shorter than that of normal beats.

The change in the duration of the refractory phase with change of rate explains an observation first made by Trendelenburg (1903). If a frog's heart is rhythmically stimulated with gradually increasing rates, the ventricle will respond to each stimulus up to a rate which, if given abruptly, would have produced half-rhythm (that is, the ventricle contracting only in response to every other stimulus). On the other hand, if with a high rate of stimulation half-rhythm was present and the rate of stimulation was then gradually decreased, whole

rhythm did not occur at a rate at which it had formerly been present, but only with a lower rate of stimulation The refractory phase accounts for these phenomena. with a gradually increasing rate the refractory period gradually becomes shorter so that successive beats tend to fall just outside the non-responsive phase, but if the rate is abruptly increased, the

is long, and a 2 : 1 response thus becomes established Similar considerations hold good for the observations made with gradually decreasing rates of stimulation.

Mines confirmed and amplified these observations He showed that, by this method, the length of the refractory period can be determined and also demonstrated that the transition from "half" to "whole" rhythm, during rhythmic artificial stimulation, can be

of the preceding beats, and although the next of the rhythmic series of excitations will fall within it, the next but one (belonging to the hitherto ' unaccented ' series) will find the tissue ready to respond. But it will also reach the ventricle sooner after a response than had an effective stimulus before, thus the refractory phase will be shorter again, and probably so short that the next stimulus falls outside the refractory phase Once started the new rhythm continues The nature of the mechanism by which one single extrasystole may under certain circumstances produce enduring effects on the heart rhythm is thus quite evident" (p 365/6) Similar conditions have been demonstrated in the frog's heart poisoned with veratrine, in which a 2 · 1 block was present (de Boer, 1915, 1916), and a similar mechanism was suggested by Scherf in order to explain the prolonged conduction in the ventricles of the second beat in clinical cases of dropped beats (Wenckebach periods) and of the difference in shape of the first of a series of extrasystoles.

The observation that the refractory phase of an extrasystole is shorter than that of normal beats was first reported by Trendelenburg in 1903 and has repeatedly been confirmed (de Boer 1915, Umrath, Lewis and Master, Schellong and Schutz, Buchthal, Andrus and Padget, Eccles and Hoff)

Schellong and Schutz investigated on heart muscle strips the relationship between refractory phase and monophasic action current, the duration of the latter could be considered to equal the duration of the state of excitation and to correspond closely to the duration of the absolute refractory phase (Adrian, 1921, Drury and Brow). The response

as the cathode of the stimulating electrodes applying the test stimulus, this arrangement made it possible to investigate the refractory period of the very site from which the action current was recorded The length of the absolute refractory period was examined by determining the shortest interval after an excitation at which a test stimulus yielded an action current The relative refractory period was measured as the smallest interval between two contractions for the second one to have an action current of the same duration as that of the preceding one. This was investigated both for excitations following maximal contraction and those following an extrasystole, in the latter event three stimuli were used and the action current of the third contraction was compared with that of each of the two preceding beats Schellong and Schutz found that the end of the absolute refractory period coincided with the end of the monophasic action current (that is, with the end of the state of excitation) An extrasystole was found to have a shorter action current and therefore a shorter absolute refractory period Comparative measurements of the relative refractory period of an

excitation following one with a normal, and one with a shortened duration of the monophasic action current, respectively, revealed that, in these two instances, the duration of the relative refractory period was the same. This means that the shortening of the total refractory phase of an extrasystole is solely due to that of the absolute refractory phase, while the relative refractory period has the same duration in normal and in extrasystolic beats. Similar conditions were found after a series of forced contractions in short succession (Pohl) and were also encountered in the auricle of the frog's heart (Buchthal).

The above conditions were established for contractions produced by induction shocks For excitations elicited by rectilinear electrical impulses the results were different: in 92 per cent. of the observations threshold stimuli were effective at the end of the monophasic action current With this kind of stimulation full excitability is regained very quickly and the end of the relative refractory period coincided approximately with the end of the monophasic action current. If contraction curves are recorded, this means that an extrasystole can be produced by a threshold stimulus shortly after the summit of the preceding systole (Schutz and Lueken)

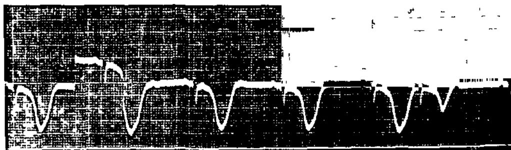


FIG 178 —The Q-T interval of the extrasystole (penultimate beat) measures 0 60 sec as compared with the 0 68 sec of the sinus beats

In clinical electrocardiography the length of the refractory period can approximately be determined by the duration of electrical systole, that is by the length of the Q-T interval. In Fig 178 the Q-T interval of the extrasystole measures 0·60 second as compared with the 0·68 second of the sinus beats (which abnormally long interval was due to myocardial damage)

Reports in the literature about the length of the Q-T interval of extrasystoles are conflicting (Fridericia; Miki, White and Mudd; Calandre and Rico). Most investigators considered the Q-T interval in relation to the preceding shortened interval, that is, the coupling of the extrasystole The lack of uniformity of the reported results is not surprising, for various factors operate in different directions in determining the Q-T duration of extrasystoles: the increased width of the ventricular complexes is apt to increase it, whereas the shortened preceding interval tends to have the opposite effect. A more recent investigation by Berliner draws attention to the fact that the QRS and the RS-T intervals of auricular extrasystoles vary independently; the RS-T intervals were found to be usually shorter than those of the normal beats though exceptions were observed; the greatest degree of shortening occurred in extrasystoles with marked widening of the QRS complexes so that the total Q-T intervals of such beats were not longer than those of normal ones. Similar discrepancies exist in regard to the Q-T interval of the first post-extrasystolic beat, with the added source of confusion that the reverse interpretation of figures was given according to whether the length of the Q-T interval was considered in relation to the long preceding compensatory

pause or to the interval between normal beats (Hegglin and Holzmann, Schlomka and Konigslow, Marx) It seems to us that the disappointing result of such determinations is only to be expected, since with abrupt change of rate the Q-T interval adapts itself to the new rate only gradually and in the course of several beats (4–10, Lepeschkin, 5–30 in the frog, Blair, Wedd and Young) Taking this observation in conjunction with the various other complicating factors, detailed above, such investigations seem rather futile

Owing to the fact that cardiac muscle has an absolute refractory period which is long as compared with that of skeletal muscle, superposition of contractions does not usually occur and extracontractions are, as a rule, not stronger than normal beats Observations of superposition of extracontractions have been reported in hearts which, for various reasons, were in a hypodynamic condition or under the influence of poisons A few examples may be mentioned: Frank (1899) reported superposition in the frog's heart if sinus and vagus were simultaneously stimulated and intraventricular pressure was low, the same phenomenon was found, also in the frog's heart, as an effect of certain poisons muscarine (Walther; Rhodius and Straub), chloral (Rohde, Schultz, Bornstein, 1906a), potassium chloride (Burridge), also cooling (Frey) Most of these authors, also Junkmann, considered a shortening of the refractory period to be the underlying factor This view was contested by Mangold and Shimizu who, by means of a pure NaCl solution without K or Ca, obtained superposition of extracontractions in the frog's heart in a high proportion of experiments (59 out of 132) They assumed that the damaged heart was only capable of partial contractions and that the superposition of extracontractions was due to the additional contraction of fibres which had not taken part in the preceding beat These authors did not therefore consider superposition as a true summation A similar view was held by Mononobe, but his experiments, interpreted to show that there was no constant relationship between the length of the refractory phase and the occurrence of superposition, are open to doubts on technical grounds

Some light was thrown on this problem by Bertha and Schutz, and by Schutz. By comparison with normal hearts the damaged one has a shorter action current and this was invariably the case in all instances of superposition of extrasystoles, that is to say, in those precipitated by induction shocks as well as in the rarer instances of spontaneous superposition In all such cases two successive monophasic action currents were recorded, each of reduced duration and amplitude Whatever the mechanism underlying superposition may be—and this remained unsolved—from an electrical point of view the phenomenon consists of two separate events following one another in close succession, mechanically,

superposition, and (2) by being higher in itself, without superposition The first variety was

der erregbaren Phase eine grossere Contractilitat besitzt als in einem spateren " p. 262)

With the heart *in situ*, or in the heart-lung preparation, once the stage of ventricular filling has started the force of a premature contraction depends largely on the initial length of the muscular fibres and thus on the degree of filling It is this factor which is of the greatest importance clinically and, in many respects, physiologically, but it is not the only one.

According to Straub, extrasystoles cause a diminished systolic power of the systolic contraction of the ventricles and a diminished output. Furthermore, with the heart *in situ* not only is the degree of ventricular filling smaller the earlier in diastole the extrasystole occurs, but also the pressure in the aorta is the higher which such extrasystolic contraction has to overcome (Wenckebach and Winterberg)

The most comprehensive and convincing investigation of the force of beats elicited by artificial stimulation is the one by Wiggers (1925) In experiments on dogs he optically recorded the pressures in the left ventricle and in the aorta, in certain experiments also in the right ventricle or in an auricle. Stimuli were applied by means of induction shocks to the left ventricle in different phases of normal beats or during artificial rhythm forced upon the heart during vagal standstill. Wiggers found that, compared with normal beats, the premature contraction had a prolonged isometric contraction phase, a slower gradient of rise of pressure and a shorter ejection phase, resulting in a *shortening* of total systole. From this it could be concluded that the smaller systolic discharge of premature beats was not solely due to the smaller pressure developed within the ventricle, but in part attributable to the reduced phase of systolic ejection Since the degree of diastolic filling and the initial tension modify not only the volume of systolic discharge, but also the duration of the ejection phase, Wiggers eliminated the first of these two factors by comparing normal and ectopic beats under conditions where initial pressures and diastolic fillings were the same. This was achieved by comparing a series of normal beats with a series of contractions artificially produced at the same rate (during vagal standstill). The result was that, with the latter rhythm, intra-ventricular pressures still remained lower and systolic discharges smaller, but total systole was *lengthened*, the phase of isometric contraction as well as that of ejection partaking. This indicated that the altered dynamics of ectopic beats were partly due to peculiarities in the nature of the muscular contraction According to Wiggers, these are due to an abnormal spread of the artificial contraction, having the result that the muscular *fractions are excited in an abnormal order or some of them not excited at all* This conception was largely based on Lewis' and Rothschild's work on the spread of normal and artificial ectopic beats Regarding the latter, these authors assumed the impulse to spread slowly through ordinary muscle until it reached the Purkinje network through which conduction, to the contralateral and most of the remaining part of the ipsilateral ventricle, was fast and occurred in the normal order (*see* section on " Spread of the Excitation of Ectopic Beats ", pp. 371–373) Wiggers' further results regarding the intraventricular pressure curves seemed to find a plausible explanation by these views Thus, if a stimulus was applied to one ventricle and intraventricular pressures were recorded simultaneously from the two ventricles, the strength of the beat of the contralateral ventricle (that is the one not stimulated) was proportionately greater than that of the stimulated one, and the gradient of pressure elevation was much steeper in the non-stimulated one. These differences were explained by the fact that the ventricle, which had not been stimulated, was activated through normal pathways and its contraction thus took place by the normal sequence of contraction of the individual fractions. This view was supported by the observation that contractions elicited very late in diastole were never quite equal in height to normal ones; in such instances it was assumed that, owing to interference of the artificial and the normal stimulus, some muscular fractions escaped being activated, or that an orderly mode of contractions may perhaps be necessary to produce a maximal effect.

Rothberger and Scherf, on the other hand, found in dogs a higher pressure in the left ventricle (optically recorded) in left ventricular tachycardia, produced by direct stimulation of the left ventricle with condenser discharges, as compared with the left intra-ventricular pressure in right ventricular tachycardia, elicited in the same way.

Wiggers also re-investigated the duration of the refractory period which, with his method of optically recording intraventricular pressure changes, he was able to do with a

greater degree of accuracy than had been possible by using mechanical records of movements during contraction He found that, while during the phase of isometric contraction and during the early stage of the ejection phase the heart was refractory to all stimuli, the absolute refractory period did not extend throughout the latter part of ventricular systole, the length of this non-refractory portion of ventricular systole covers, on an average, the last 0 06 second before the termination of systole No evidence of superposition of such contractions elicited during the latter portions of systole was found and reports of such superposition were attributed to faulty technique or to a grossly abnormal condition of the heart Wiggers gives reasons for the belief that the contraction resulting from such early stimuli is not due to excitation of fibres which are already relaxed, but to disappearance of the state of refractoriness during the latter part of contraction

As far as a moderately strong, brief D C. shock is concerned, which was applied considerably before the T wave of an electrogram recorded at, or near, the point of stimulation, Moe, Harris and Wiggers (1941) found that a stimulus of this kind and timing produced one

to such early stimuli is probably not due to an actual systolic excitation, but to the creation in the tissues of a decrementing polarization potential which is sufficient in duration and in intensity to excite early in the next relatively refractory phase

To return to Wiggers' work on the dynamics of artificially induced contractions just after the isometric relaxation phase, a small difference in the time of the premature contraction produced marked changes in the pressure maximum of the premature beat, this is due to the influence of filling with the resultant increase in the length and tension of the muscular fibres

Regarding the factors which determine the effectiveness of premature contracions, according to Wiggers effective premature contractions—that is, those producing ta rise in intraventricular pressure sufficiently high to eject blood into the aorta—are recognized·

(1) by the production of a clear cut aortic pulse,

(2) by the fact that the intraventricular pressure rises beyond the point where ejection normally takes place,

and

(3) by the sharper drop in pressure during the isometric relaxation phase, indicating that the contraction had not been of an isometric character

The fundamental factor which determines whether or not a premature contraction is effective is a minimal interval of ventricular filling; on an average this was found to be 0·12 second between the end of systole and the onset of the premature contraction Since the interval between the beginning of diastole and the opening of the A-V valves measures about 0 08 second, a minimal interval of about 0 04 second is required for a degree of ventricular filling adequate to cause ejection against normal arterial diastolic pressure. The actual length of this interval depends on the height of diastolic pressure and the rate of ventricular inflow

This effect of rate upon presence or absence of ejection is well shown in the study of Coblentz *et al* These authors catheterized adult patients with various cardias lesions and recorded intra-ventricular, and sometimes also pulmonary artery, pressure curves, and electrocardiogram

at various phases of

or right) ventricular

0 640 second at 58 beats per minute; this relationship was found to be linear (their Fig 11 on p 12).

Of the various points arising from Wiggers' extensive studies we should like to emphasize:

(1) once ventricular filling has started, its degree largely determines the height of intraventricular pressure produced by the premature contraction;

(2) in addition to (1): the mechanism of a premature contraction due to an ectopic impulse differs from that of normal beats in such a way that the pressure maximum of an ectopic beat tends to be lower than that of a normal beat originating in otherwise identical conditions,

(3) in addition to (1) and (2): the smaller systolic discharge of a premature contraction is partly attributable to the shorter phase of systolic ejection of the premature beat.

A more recent clinical observation is in accordance with Wiggers' experimental findings By optically recording the pressure changes in the brachial artery in patients with auricular fibrillation Buchbinder and Sugarman showed that the duration of the preceding cycle length was the most important factor determining the degree of pressure changes; if extrasystoles occurred in such cases, they produced a rise in diastolic and fall in systolic pressure which were too great as to be explained solely by the short cycle length preceding the ectopic beat extrasystoles occurring not more prematurely than some of the conducted beats produced so small an increase in intra-ventricular pressure that such contractions had no appreciable influence on the pulse curve, that is, failed to open the semilunar valves. This seems to be an instructive confirmation of Wiggers' views that the abnormal mechanism of the premature contraction is an important factor accounting for the reduced efficiency of such beats. The fundamental mechanism seems to be the " less perfect summation of fractionate contractions when the excitation waves spread from a ventricular focus, and in part to a less efficient mechanical twist of the ventricular muscle scrolls when the septum is not excited first " (Wiggers, 1944). Differences, between normal and ectopic beats, in the rate *and sequence of activation of the various portions of the heart can be expected* to be of importance also from a different point of view H. C. Wiggers (1937) has shown that the impulse of normal beats reaches all parts (except one area) of the ventricles within about 0 005 second, that is, practically simultaneously (*see also* section on " Spread of the Excitation of Ectopic Beats ", p 370). On the other hand, Ashman and Hull calculated that it takes at least 0 035 or 0·04 second, possibly more, for an impulse to travel from the Purkinje network in a lateral ventricular wall to the bifurcation of the bundle, and that conduction by way of the interventricular septum does not take less time than via the bundle branches and bifurcation It seems reasonable to assume that such great differences in the rate of activation of the various portions of the heart play an important part in accounting for the differences in the dynamics between normal and ectopic beats

Investigations in man about the length of the isometric contraction phase of extrasystoles seem, on the whole, to be in accordance with the experimental findings. Blumberger, and Blumberger and Meyer found that, with rare exceptions, extrasystoles, particularly ventricular ones, have a lengthened isometric contraction phase. Their ejection phase was shortened The first post-extrasystolic beat showed the reverse alterations in the lengths of these intervals

More recently Weissel and Vetter pointed out that it is an unjustifiable simplification to designate as "Anspannungszeit"* the interval between the beginning of electrical activation

of the ventricles and the opening of the semilunar valves, since there is a distinct interval between the beginning of electrical activation (beginning of the Q or R wave) and the beginning of the steep rise in intra-ventricular pressure. They termed this interval "elektropressorische Latenz" (electro-pressor latent interval) In nine patients with congenital cardiac lesions, in whom they recorded intracardiac pressure curves and electrocardiogram, they found that extrasystoles had a shortened "isometric contraction phase" whereby the electro-pressor latent interval as well as the isometric contraction phase in its purely mechanical sense partook Both these phases were found shortened in the first post-extrasystolic beat. Coblentz *et al*, on the other hand, found the interval between Q and the beginning of right ventricular systole (corresponding to Weissel and Vetter's electro-pressor latent interval) of ventricular extrasystoles normal in nine cardiac patients

We consider it desirable to make a brief reference to this recent work as it illustrates the difficulties in determining these various phases of cardiac contraction in man and also supports our doubts about the applicability to clinical problems of Blumberger's work in its present stage (*see* below, p 364), this author identifying the moment of beginning mechanical with that of electrical systole

The Post-Extrasystolic Beats

The first post-extrasystolic beat usually is stronger than the normal beats of the individual case This was first reported in the isolated heart of the frog by Langendorff in 1885 and considered by him to be a vagal effect, a view which he subsequently abandoned (*see* below) The same was found to prevail in the mammalian heart by McWilliam and by Gley and studied in more detail by Langendorff (1895 and 1898) Langendorff found that the smaller the extrasystole, the larger the first post-extrasystolic beat and interpreted this observation as indicating a compensatory phenomenon, effecting a constancy of work, equal amounts of energy being developed during equal periods While this explanation proved untenable, the observation was confirmed by various authors (for example, on the bloodless amphibian heart by Bottazzi, on the mammalian heart by Cushny and Matthews)

Woodworth investigated this phenomenon in more detail on the spontaneously beating apex of the dog's heart He found that the first post-extrasystolic beat was stronger than the normal "almost without exception", its average height being 124 4 per cent. of that of the normal beats The earlier the extrasystole the higher the first post-extrasystolic beat tended to be, and the degree of prematurity was more important than the length of the post-extrasystolic interval Even if the latter was not longer than the interval between normal beats, the post-extrasystolic beat was stronger and this was attributed to a strengthening effect of the extracontraction. Woodworth also found that two successive extracontractions tended to be followed by an exceptionally strong post-extrasystolic beat and that several post-extrasystolic contractions may show increased height In the frog's heart, on the other hand, the greater height of the post-extrasystolic beat was found to be due to the preceding pause and no effect of the premature beat itself, as was established in the dog's heart, could be traced This difference between the two species was attributed to the slower rate of the apex of the dog's heart as compared with that of the frog's ventricle

Rihl (1906), confirming Woodworth's findings in the mammalian heart, concluded that the greater height of the first post-extrasystolic beat depended solely on the prematurity of the extrasystole and on the length of the post-extrasystolic interval, the ectopic origin of the premature contraction was thought to be without importance, since premature nomotopic beats had the same effect Again in accordance with Woodworth, Rihl found that the prematurity of the extracontraction was the salient factor, for a higher first post-extrasystolic contraction was observed also after an interpolated extrasystole, an observation later confirmed by Busquet and Tiffeneau Bornstein's (1906c) objection that the coronary circulation

was the underlying factor accounting for Rihl's observation is unacceptable because of Woodworth's results on the isolated apex. Moreover, as early as 1888 McWilliam had observed the phenomenon in the mammalian heart when superior and inferior vena cava were clamped and the ventricular cavities were no longer distended with blood.

Regarding the height of the subsequent post-extrasystolic beats conflicting findings were published. Rihl found that in some experiments they were of increased, in others of reduced height. An increased amplitude of the second post-extrasystolic beat was reported by Busquet and Tiffeneau. A gradual increase in the height of several post-extrasystolic beats, reminiscent of the staircase phenomenon, was found by Goteling Vinnis in the radial pulse tracing of a patient.

Regarding the underlying mechanism of the stronger first post-extrasystolic beat, the greater degree of diastolic filling is the most important factor. In certain conditions, however, this explanation cannot hold good, for instance, in the case of interpolated extrasystoles followed by a post-extrasystolic beat with increased amplitude. Busquet and Tiffeneau put forward good reasons for the assumption that, in such circumstances, the phenomenon is due to an increase in contractility whereas an increase in excitability could be excluded.

Regarding the Q-T interval of the first post-extrasystolic beat, *see* above (p. 358).

At present, the investigations of the dynamics of premature contractions and post-extrasystolic beats are only of physiological interest. Attempts at applying them clinically for assessing the diagnostic and prognostic significance of extrasystoles in individual cases have been made (Blumberger, Blumberger and Meyer, Breu and Vetter), but the premises on which the measurements of the various phases of systole, and the interpretations of their results were based are open to so much doubt that, at this stage, the validity of this method in clinical medicine seems highly questionable.

SUMMARY

The force of an artificially induced cardiac contraction is independent of the intensity of the stimulus. Some apparent exceptions to this all-or-none law with their explanation are briefly discussed. Owing to the fact that, after a contraction, the heart regains its excitability gradually in the course of the relative refractory period, in general an extra-contraction is the weaker the earlier in diastole it occurs. For the same reason an extra-contraction can be elicited the earlier in diastole the stronger the extra-stimulus is. The refractory phase decreases in length with increasing rate, and that of an extrasystole is shorter than that of normal beats. The shorter total refractory period of an extrasystole elicited by an induction shock is due solely to its shorter absolute refractory period, whereas the relative refractory period of an extrasystole has the same length as that of a normal beat. Approximate determination of the length of the refractory period of extrasystoles in clinical electrocardiograms by measuring their Q-T intervals has given conflicting results. The reasons for the discrepancies are discussed and it is suggested that such investigations are devoid of any great importance. The conditions in which superposition of extrasystoles may occur and the possible mechanism underlying this phenomenon are briefly reviewed. Discussion of the dynamics of premature contractions is largely based on Wiggers' extensive work. It is pointed out that, in addition to the degree of ventricular filling largely determining the force of extracontractions, their mechanism differs from that of normal beats in such a way that it tends to reduce the force of an ectopic beat as compared with that of a normal beat originating in otherwise identical conditions. This aspect is discussed in some detail.

The first post-extrasystolic contraction is usually stronger than the normal beats of the individual case. This is largely due to the greater degree of ventricular filling which had

taken place during the preceding longer post-extrasystolic interval. In certain circumstances this explanation cannot hold good, for instance, in the case of a larger post-extrasystolic beat following an interpolated extrasystole, and an increase in contractility of the heart seems the most likely explanation

It is pointed out that, at present, attempts at applying the experimental findings of the dynamics of premature contractions to the clinical assessment of the diagnostic or prognostic significance of extrasystoles have not yet yielded reliable information

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INTENSITY OF ECTOPIC STIMULI

At one time the intensity of the stimulus giving rise to ectopic beats attracted much attention A brief discussion of the work on this subject is warranted because some of its results enlarged our knowledge in several important respects though most of the original conclusions have become questionable. In the light of more recent work much, if not most, of this work requires re-interpretation.

The intensity of extrasystolic stimuli was frequently assessed with reference to that of the normal ones and a few salient points of the work on the latter subject must therefore be included

While the natural stimuli were originally thought to be very weak, of threshold intensity (Engelmann, 1894, 1896, Gaskell), or of "phasic threshold intensity", that is, responding to the phasically varying excitability of the heart (Hering, 1906), a great deal of evidence accumulated subsequently which tended to show that the strength of normal stimuli was many times above threshold. Amongst the numerous publications on this subject those are relevant, in the context of this book, which base this conclusion on a comparison between normal and artificial stimuli applied in different experimental conditions, the greater strength—or qualitative superiority—of normal as compared with artificial stimuli was inferred from the observation that the heart continued to beat in response to normal impulses while artificial stimulation even with strong stimuli failed to have any effect Such observations were made on frog hearts beating under anaerobic conditions (Bachmann) or under the influence of an excess of KCl (Bunnag); the results of such studies were summarized by Asher in whose laboratory much of this work had been carried out In the same Institute it was subsequently found by Witz that local anaesthesia by novocaine of the auricle or sinus of the frog heart could produce a condition in which the normal heart action continued while the anaesthetized part failed to respond to strong artificial stimuli By a different approach Schellong—investigating the gradient of rise of the action current—
[illegible]

because of its considerable intensity, would, if it occurred at that moment, also yield a contraction This assumption was shown to be correct by Schutz and Buchthal who found that, if the rate of normal impulse formation in the frog heart was increased by warming, the earliest moment at which normal stimuli became effective also coincided with the end of the absolute refractory period From this it was concluded that the intensity of the normal stimuli must also be at least four times that of threshold. Rothberger (1931a) observed that, after interpolated extrasystoles, the next supraventricular beat may start before the end of the T wave of the extrasystole in the electrocardiogram and concluded, with certain reservations, that the strength of the natural stimulus is considerably above threshold (*see also* p 369) A similar view was expressed by Junkmann, based on the observation that auricular extrasystoles yield a contraction already at a time when strong stimuli are necessary to stimulate the ventricle directly

While the results of such investigations are of considerable interest in themselves, their interpretation in regard to the intensity of natural and artificial stimuli is no longer acceptable in its original form for various reasons:

(1) In all experiments discussed above, induction shocks were used as artificial stimuli. Such faradic shocks are of very short duration and their characteristics (for example, voltage, duration) were unknown A so-called calibration of such currents according to an arbitrary scale (for example, Kronecker units) is as meaningless in experiments of this kind as it is valueless for any general theory of excitation (Schaefer, 1940).

(2) The duration of the artificial electrical stimuli was not considered

(3) The effectiveness or otherwise of natural and artificial stimuli was predominantly attributed to the intensity of the stimulus and not sufficient consideration was given to the excitability of the tissue.

Amongst the studies of cardiac excitability, in which a well-defined electrical stimulus of known duration was used, that of von Werz may be mentioned This author studied the chronaxie of the frog's ventricle during the relative refractory period (chronaxie being the minimum time during which a current of double the rheobasic strength must flow in order to excite, a current has rheobasic strength if it is just capable to excite when flowing for a long time). The chronaxie is a measure of excitability inasmuch as the shorter the chronaxie the more quickly excitable the tissue. In von Werz's experiments the ventricle was rhythmically stimulated (by induction shocks) and condenser discharges were applied as test shocks during the various phases of the relative refractory period. It was found that immediately at the end of the absolute refractory period the chronaxie was lengthened two to three times and that it returned quickly to its original level during the relative refractory period Regarding test stimuli of the same absolute intensity von Werz also established that the longer above the utilization time their duration was, the earlier in the relative refractory period did they produce an extrasystole (utilization time being the minimum time during which a current of rheobasic strength must flow in order to excite) At the end of the relative refractory period a natural stimulus of minimum intensity will be effective if its duration is at least equal to the utilization time of ventricular excitation. Von Werz pointed out that, because of their short duration, induction shocks are inferior to natural stimuli even if the chronaxie is not lengthened, and even more so if this is the case (for example, because of digitalis), and concluded that the natural stimuli are of comparatively long duration, but less intense than commonly believed. Von Werz's results conflict with those of Asher who found no difference between the effectiveness of condenser discharges of long duration and of induction shocks Further investigations are necessary before this problem can be considered as settled.

One instance of the different effect of induction shocks and of rectilinear currents is discussed in connexion with the determination of the refractory period (*see* section on " Dynamics ", p. 358).

At present we have no information about the strength (or even nature) of the natural cardiac stimulus In order to gain some insight into the intensity of stimuli necessary to elicit ectopic beats comparison was made between the effectiveness or otherwise of artificial stimuli and that of natural ones. The criterion usually was whether the heart continued to beat in response to its natural impulses while artificial stimuli, applied in different phases of diastole and in different experimental conditions, were ineffective, or vice versa (Asher and Garrey) It will be seen from what was said above that such investigations, if they are to supply any information in keeping with more recent neurophysiological work on excitation, must at least employ an artificial stimulus which is well defined and the strength and duration of which are known Moreover, the excitability of the stimulated portion of the heart must be more fully considered than has been the case in some of the work discussed, and some quantitative information about it should be available. One such expression would be the chronaxie (*see* Rijlant), though its determination, and that of the rheobase, in the heart meets with great difficulties (Schaefer, 1942).

Some of the more recent work, which has a bearing on the subject under consideration

and fulfils the above conditions, is discussed in the chapter on " Mechanism " to which the reader is referred (p 497)

Turning to the data about the presumed strength of stimuli giving rise to extrasystoles in man it has to be admitted that most of it is speculative Kaufmann and Rothberger assumed that such extra-stimuli are weak, just above threshold, and based this opinion on the observation that in subjects with pronounced sinus arrhythmia extrasystoles tend to occur most frequently when the sinus rate is about midway between more marked tachy- and bradycardia The tentative explanation was that, in order for extrasystoles to occur, a certain degree of sympathetic nervous tone was necessary, so that extrasystoles tended to disappear whenever sympathetic tone decreased or vagal tone increased Winterberg endeavoured to explain a periodicity of cardiac rhythm, consisting of periods of supraventricular tachycardia separated by two or three slow normal beats, by the assumption that the stimuli precipitating the fast series were just above threshold and that, as the result of their quick succession, the excitability of the heart slightly decreased so that the weak ectopic stimuli became sub-threshold and the stronger normal stimuli dominated the rhythm for a few beats (In retrospect, this seems to have been a case of " Extrasystolie à paroxysmes tachycardiques ", occurring in an otherwise healthy male of twenty.)

The opposite view, namely, that extrasystolic stimuli must have a considerable strength, was put forward by Rothberger (1931b) because of the observation that interpolated extrasystoles may commence before the end of the T wave of the preceding supraventricular beat had been completely inscribed In the light of more recent knowledge such observations seem far better explained by attributing them to the varying excitability of the tissues following excitation, in particular to the supernormal phase of recovery, and the same holds good for the observations of Rothberger (1931a) mentioned above Thus Smirk, who recently published seventeen cases in which R waves interrupted T waves, interpreted his observations entirely in terms of cardiac excitability

Scherf emphasized the complexity of factors which determine whether or not an ectopic focus becomes effective and stressed the importance of excitability, strength of stimulus, nervous influences and ionic concentration Similarly, Faltitschek and Scherf attributed the presence or otherwise of an exit block in parasystole to the relationship between strength of impulse formation in the automatic ectopic centre and the excitability of the surrounding tissue (*see* chapter on " Pararrhythmias ", p 173).

Conclusions It seems to us that neither experimental nor clinical observations make it possible to draw any reliable conclusions about the strength of a stimulus, normal or ectopic Schellong's statement of 1925 still holds good " As one has to measure the stimulus by its effect, namely excitation, and up to the present no feature of either the mechanical or the electrical manifestation of excitation can unequivocally be attributed solely to the strength of the stimulus, any views about it are nothing more than suppositions " (our translation)

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THE SPREAD OF THE EXCITATION OF ECTOPIC BEATS

The development of our ideas about the mode of spread of the excitation of ectopic beats reflects the gradual recognition of the great complexity of this subject which, in the past, appeared comparatively simple

The starting point may be placed in the work of Marchand (1877) and Engelmann (1878) who established in frogs that, if a point on the heart's surface is stimulated and the action currents are led off from two places, the one situated nearest to the point of stimulation becomes electrically negative in advance of the other situated at a greater distance [illegible]

(1906) expressed the opinion—which ran contrary to the conception of contemporary physiologists—that the specialized fibres conducted the impulse faster than the ordinary myocardial fibres

Kraus and Nicolai, in developing this conception, distinguished between normal systoles and abnormal ventricular beats (normale Systolen und abnorme Ventrikelschläge). They considered the essential difference to be that the impulses of the former were conducted in the ventricles through preformed pathways, whereas the latter spread evenly in all directions without using any preformed channels of conduction ("gebahnte" und "ungebahnte" Reizausbreitung) By leading off the action currents from a series of very small areas of the cardiac surface by means of a specially designed cotton thread electrode (called differential electrode) it was subsequently established in the frog and tortoise (Clement) and in the mammalian heart (dogs and cats, Erfmann) that the normal excitation activates the whole cardiac surface practically simultaneously whereas ventricular ectopic beats, elicited by break shocks, spread from points nearer the site of stimulation to those situated at a greater distance. Rothberger and Winterberg, as a result of their investigations on the shape, in the electrocardiogram, of ventricular extrasystoles elicited in different parts of the

dog's heart (discussed in the chapter on "Local ... on pp. 382–4), concluded that the excitation ... muscle to the nearest ... and that it was this ...

In Lewis' and F ... study (... ave through the ventric... in dogs, that of ecto... t of this work, as far as it ... in Lewis's ow

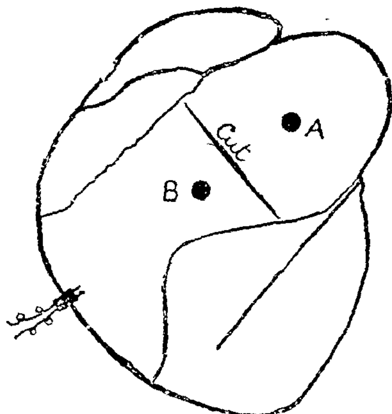


Fig 179 —From Lewis, *The Mechanism and Graphic Registration of the Heart Beat* Third ed, 1925 Shaw and Sons, London
Description in text

"If an artificial wave is started ... electrodes ... can be ac... ... of the ventricular ... or surpasses 2,000 mm per second wh... is lowest and approaches 400 mm per second where the ... thickest It varies because the rate of conduction in muscle proper is slow, while in Purkinje substance it is very rapid If the wall is stimulated where it is thin, the artificial wave quickly penetrates the whole muscle thickness and is picked up and conveyed along the Purkinje network, from which it spreads outwards through the muscle again to reach the electrodes; if, as in the left ventricle, the wall is thick, the wave may be

conducted across the superficial electrodes before it travels to the lining of the heart and out again. These conclusions follow from experiment. The border of the right ventricle is stimulated and an excitation wave is propagated *from B to A; its arrival at the* two points is timed. A deep cut in the muscle between the electrodes does not affect these readings; a shallow cut or scratch on the endocardial surface at once delays the wave reaching B. Clearly the wave passes along the endocardium over the greater part of its course." (Fig. 179)

"If electrodes are placed on the pericardial surface (P) and on the *corresponding part* of the endocardial lining (E) and the surface is then stimulated at some distance from them"

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is the quicker on account of the high conduction rate in the lining If the stimulus is applied

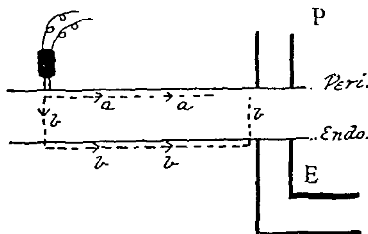


FIG 180—From LEWIS, *The Mechanism and Graphic Registration of the Heart Beat* Third ed, 1925 Shaw and Sons, London
Description in text.

nearer the electrodes, the wave may reach P along the path a-a If the thickness of the muscle wall, and the distance from the point of stimulation, is known, then in an experiment in which the natural *readings at the two contacts are just maintained, the relative rates of con-*duction in Purkinje substance and muscle can be calculated. The rate is at least five times greater in the network than in the muscle. The experiment is arranged so that the wave reaches P along the two paths a-a and b-b simultaneously; the length of muscle traversed along b-b is ascertained and from these data the conduction rates are calculated. When the results of experiments of this and other kinds are considered, it is found that in muscle the rate of conduction is about 400 mm. per second; in *straight*, as opposed to the usual branching, Purkinje strands it is approximately 4,000 mm. per second"

This view, that *the rate of conduction in the Purkinje substance is ten times that in the* myocardium proper, was contested by various authors on various grounds

de Boer questioned altogether that the velocity of the excitation wave is greater in the ... ference
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conduction than the myocardium proper, found the former to be only 730–740 (Erlanger) or 500 mm. per second (Lapicque and Veil) Both these series of experiments were, however, conducted under rather unphysiological conditions and cannot be expected to yield more than very approximate results; Lewis remarked that Erlanger's figure is likely to be too small (Lewis, 1925b) In view of the subsequent discovery of myocardial ramifications of Purkinje substance the meaning of some of these figures has become questionable Another objection, based on quite different grounds, was raised by Rothberger He pointed out that, if the rates of conduction in the specialized system and in ventricular muscle were in the proportion 10 . 1, in cases of intraventricular disturbances of conduction in man initial ventricular deflections of 0·2–0·5 second would have to be found, which has never been the case

If the actual velocity of conduction in the specialized system and its exact relation to that in heart muscle proper was thus controversial, two main facts seemed established first, that the Purkinje fibres conducted faster than the myocardium, and second, that a forced ventricular beat was slowly conducted through the heart muscle until it reached the nearest point of the specialized system whence the fast conduction started to the remaining parts of the ventricles In order to reach the opposite ventricle the excitation wave was assumed to travel in a retrograde direction through the ipsilateral branch of the stimulated ventricle as far as the bifurcation and thence to activate the opposite ventricle by spreading in the normal way through the contralateral main bundle branch and its ramifications.

Observations on interpolated ventricular extrasystoles were in accordance with this conception As discussed in the appropriate section, the first post-extrasystolic beat after interpolated extrasystoles frequently shows a lengthened A-V conduction time, but often has a normal shape in the electrocardiogram Ashman pointed out that the blocking of the interpolated extrasystole must therefore occur either in the main stem of the bundle of His or within the A-V node itself, because, if the blocking occurred below the bifurcation, the ventricular portion of the post-extrasystolic beat could not be normal, but would always have to be aberrant because of altered intraventricular spread of the excitation That ventricular extrasystoles are conducted over a longer or shorter distance through the bundle branches, probably as far as the A-V node, also follows from their effect on A-V rhythm (*see* section on " Extrasystoles in A-V Rhythm and Return Extrasystoles ", p 102)

However, when it became possible experimentally to produce chains of extrasystoles originating from one circumscribed focus in a ventricle and thus to put these views to experimental test, some rather unexpected results were obtained For if the above conception

whatever the method by which the chains of ectopic beats were produced

lati

electrocardiogram remain unaltered after cutting the ipsilateral bundle branch between its upper and middle third, but also severing of both main branches did not affect their graphic record though complete A-V block ensued (Fig 181, Scherf, 1926)

(2) Chains of ectopic beats were elicited by local warming of a point on a ventricle in dogs sensitized with barium Again severing of one or both bundle branches

this form, too, of an ectopic ventricular arrhythmia, caused by true extrasystoles in the

strict sense of the term and originating in one focus of one ventricle, no effect on the electrocardiographic appearance of the extrasystoles by unilateral or bilateral severing of main bundle branches was observed The coupling of the extrasystoles, however, showed certain analysable and instructive changes: if the bundle branch of the contralateral ventricle was severed, the coupling remained the same as it had been before the interference, if, on the other hand, the bundle branch of the ipsilateral ventricle was cut, the coupling increased by 0 035 to 0 04 second (*see* Fig. 125) From this observation it could be concluded that the length of the coupling depended entirely upon the exact moment at which the excitation wave reaches the focus of origin of the extrasystole, which moment is itself dependent, *inter alia*, on the length of the path which the excitation wave utilizes to reach the extrasystolic focus (Scherf, 1930)

Scherf concluded from the results of these three series of experiments that ectopic ventricular beats, whether elicited by artificial stimulation or originating spontaneously in certain experimental conditions, spread through the myocardium proper and do not utilize the larger branches of the specialized conducting system

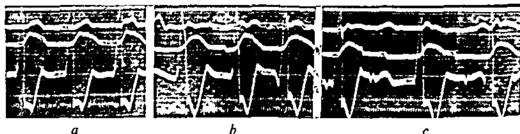


FIG 181 —From an experiment on a dog's heart *in situ* Tracings from above downward signal, suspension tracing of auricle, suspension tracing of [illegible]

A view intermediate between that of Lewis and Rothschild and that of Scherf was adopted by Drury and Mackenzie In experiments on dogs these authors produced ectopic beats in the left ventricle and recorded the arrival of the excitation wave in different portions of the right ventricle before and after cutting of the right bundle branch Such experiments demonstrated that *some* parts of the right ventricle were activated via the bundle and *some* parts via the ventricular muscle proper. It should be noted that a difference of 0 005 second in the relative occurrence of laevo- and dextrocardiogram is sufficient to produce noticeable changes in the electrocardiogram, so that an effect of this order, caused by the cutting of a bundle branch, would have been traceable. No effect of vagal stimulation was found on conduction either through the bundle branches or through ventricular muscle. It was concluded that the mode of activation of the contralateral ventricle by an ectopic ventricular beat is the result of a race between an impulse travelling via the specialized system and one utilizing myocardial muscle

It will be appreciated that the interpretation of all the work, discussed so far, was based on the assumption that no communication existed between the right and left bundle branch and their arborizations. The absence of such connexions was specifically mentioned by Lewis (1925c) The subsequent discovery of such links, while clarifying some discrepancies, revealed the great complexity of this subject.

The first to demonstrate septal connexions between the Purkinje fibres of the two ventricles of the heart of calves, particularly in the apical portions of the septum, was Wahlin (1928, 1932) Cardwell and Abramson, and Abramson and Margolin confirmed this in the heart of other mammals and also showed that Purkinje fibres extended throughout the myocardium to within a few mm of the epicardial surface. These were directly continuous and structurally identical with those of the subendocardium.

In the light of this wider distribution of the Purkinje substance Rothberger re-investigated the problem in 1933. While confirming Scherf's observations, discussed above, he thought that their interpretation had to be revised The failure of cutting one or both bundle branches to affect the shape of ectopic beats in the electrocardiogram could no longer be taken to indicate spread through the ventricular muscle proper, as Scherf had done before the presence of septal connexions between the Purkinje network of the two ventricles was

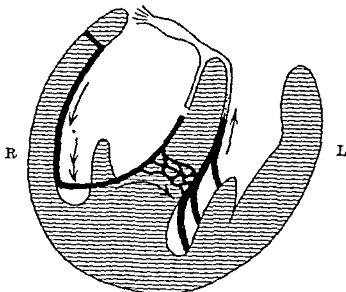


Fig 182 —The effect, upon the spread of an ectopic impulse, of cutting a bundle branch at different levels For further description, see text From Rothberger, 1933 *Z ges exp. Med*

known The site at which Scherf cut the bundle branches (between the upper and middle third, as mentioned above) was too high to block the interseptal connexions (Fig 182). Rothberger showed that, if the conducting system was severed at a point so that these were blocked, a considerable widening of the initial ventricular complexes of the ectopic beats ensued (from 0 08 to 0 12 and 0·125 second) By this experimental interference the impulse *is forced to leave the specialized conducting system and travel through ventricular muscle* proper over a certain distance These experiments had also a bearing on a re-interpretation of curves of so-called arborization block. A more detailed discussion is outside the scope of this book and the reader is referred to Rothberger and to Mahaim

The importance of the interseptal connexions for the conduction of normal as well as of ectopic ventricular impulses was also stressed by Abramson and Jochim They found that the average time consumed in the spread of an artificially induced stimulus over a constant epicardial distance on the right ventricle was only slightly less than on the left one; this

observation is contrary to Lewis' and Rothschild's conception that the impulse penetrates the ventricular muscle proper at a slow rate and is subsequently conducted through Purkinje substance at a much faster rate, then to traverse the muscle again slowly to reach the epicardium. " By obtaining the times of arrival of artificially induced ectopic impulses at various spots before and after cutting the right branch of the bundle of His, evidence was found which indicated that the impulse originating on one ventricle might reach the opposite one through the myocardial Purkinje fibres in the septum, rather than over the bundle branch pathway via the bifurcation of the bundle of His " (p 647) Their investigation did not support the contention of Robb and Robb that the impulse spreads through the superficial spiral muscle in the direction from apex to base, or that the superficial muscle bundles determined in any way the spread of the excitation wave.

Ashman and Hull compared the widest QRS complexes seen in extrasystoles in a normal heart with those found in bundle branch block and concluded that " it takes at least as long for an impulse to travel from one ventricle to the other by way of the bundle branches and bifurcation as by way of the interventricular septum ". They calculated that conduction of an impulse from the Purkinje network in the lateral wall of the ventricles to the bifurcation takes at least 0 035–0 04 second, the delay is assumed to occur mostly in the proximal part of the bundle branch

A word of warning should be given against accepting too readily the existence of trans-septal connexions or, if their anatomical presence is considered established, against overrating their physiological function. As far as the anatomical work is concerned, much of it was carried out by means of an injection technique which cannot be considered to give entirely reliable results The histological differentiation between specialized and ordinary myocardial fibres is notoriously difficult. Moreover, results obtained in one species cannot unreservedly be applied to others In this connexion the experimental work of Alfredson and Sykes is of interest. They found in experiments on calves that cutting of a bundle branch resulted in only a very slight increase (0 01 second) in the width of the QRS complex as compared to conditions prevailing in the dog and in man The most likely explanation is that in the heart of oxen functioning trans-septal connexions are present which do not exist in the dog or in the human heart. This view is supported by the observation that, in spite of the larger size of the ox's heart, the width of the QRS complex in this species is almost the same as it is in the dog and in man. Further studies are necessary before the anatomical existence and physiological significance of trans-septal connexions can be considered established

With these reservations Rothberger's views can be said aptly to sum up the physiological significance of the trans-septal Purkinje fibres. According to him these fibres normally serve to activate the septum and, in addition, provide a safety mechanism in the event of disturbances of conduction in the bundle branches. If the normal paths are intact these septal connexions are not utilized. The possibility of trans-septal activation in case of need may be likened to that of A-V impulse formation in the event of failure of normal impulse formation in the S-A node, or the presence of collateral blood vessels not utilized until the normal channels of circulation fail in their proper function.

It will have become apparent that the problem of the manner of spread of ectopic beats is far from solved. This is understandable if the great difficulties in ascertaining the exact sequence of activation of the various portions of the ventricles in normal beats are recalled. One of the main problems in this kind of work is the determination of the moment of [illegible] deflection

[illegible]

trode. The validity of Wiggers' method was challenged when it was found that (particularly

when Wiggers' technique for obtaining monophasic action currents was used) the injured region becomes electrically positive as the result of activity of the surrounding myocardium (Eyster, Meek, Goldberg, and Gilson); and a more recent investigation by Harris, while being partially in accord with that of Lewis and Rothschild, seemed to indicate that the different size of the heart in different species is of importance regarding the intervals between the activation of the several portions of the ventricle Still more recently it has become altogether extremely doubtful whether the tip of the R wave indicates the arrival of the impulse beneath the exploring electrode and the validity of the whole method has thus been rendered highly uncertain

It seems to us that such investigations have an important bearing on the subject of this

seem to be the next step in the elucidation of this problem.

SUMMARY

When the advent of electrocardiography made it possible to examine experimentally the mode of spread of the excitation wave of ectopic ventricular beats in the mammalian heart, the result of such investigations was interpreted as indicating that the excitation spreads

from within outwards It was believed that the rate of conduction in ventricular muscle proper was considerably lower than in the Purkinje substance, but differences of opinion existed as to the relation between the two rates of conduction, and regarding the velocity of spread through the Purkinje network The failure, by cutting one or both main bundle branches, to affect the shape in the electrocardiogram of artificially elicited or of spontaneous ventricular ectopic beats was first interpreted as indicating that the ectopic impulse utilizes only ventricular muscle in order to reach the opposite ventricle This view had to be abandoned in the light of the subsequent discovery of trans-septal connexions between the Purkinje network of the two ventricles. The further discovery that Purkinje fibres, continuous and structurally identical with the subendocardial ones, extended throughout the myocardium to within a few mms of the epicardial surface created further difficulties in any longer accepting the view that conduction through ventricular muscle was much slower than *through the specialized conducting system Re-investigation of the sequence of surface activation* by means of monophasic action currents suggested the necessity of revising our conceptions about the spread of normal excitation to the various portions of the ventricular surface which, contrary to previous views, seems to be activated practically simultaneously in its entirety (except for one small portion) As the result of later investigations this view was challenged on technical grounds The doubts which have been cast by these more recent anatomical and physiological studies upon the views about the mode of spread of ectopic impulses through the mammalian heart are so great that this problem cannot be considered as clarified The present state of our knowledge may be summed up by the following tentative suggestion which does not seem to conflict with any established facts: If the conducting system is intact, the ectopic impulse spreads from the point of origin through ventricular muscle proper and the myocardial ramifications of Purkinje substance

to and through the ipsilateral main bundle branch as far as the bifurcation and thence activates the opposite ventricle through normal pathways; the rate of conduction through ventricular muscle proper is, however, not so much slower than in the specialized conducting system as originally believed. In the event of interruption of conduction in one or both main bundle branches the excitation wave utilizes trans-septal connexions between the Purkinje networks of the two sides In case of impairment, but not complete interruption, of normal conduction the activation of the opposite ventricle is the result of a race of the excitation wave travelling through the bundle branches on the one hand, and through trans-septal connexions on the other

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MISCELLANEOUS PHYSIOLOGICAL CONDITIONS

Extrasystoles in Animals

Though our knowledge about the occurrence of extrasystoles in normal animals and in association with various diseases is scanty it can be said that spontaneous ectopic arrhythmias are certainly uncommon in most animals used in laboratory experiments, since otherwise their presence would have been reported far more frequently.

One possible exception are rabbits which sometimes show spontaneous extrasystoles, and which are prone to develop this type of arrhythmia as a result of drugs and vagal reflexes Regarding the former, morphine should be mentioned especially (Ken Kuré, Hering), regarding the latter the reader is referred to the chapter on "Extrasystoles and the Nervous System"

As far as dogs are concerned, in more than one thousand experiments on animals anaesthetized with ether or a barbiturate we did not encounter one single instance of spontaneous extrasystoles Lannek considers even single auricular or ventricular extrasystoles as definitely pathological and comparable, in this respect, to heart block

In the horse extrasystoles are uncommon (Lewis) and seem to have a similar significance Amongst a hundred cases of arrhythmias observed in horses, Norr encountered fifteen instances of extrasystoles, 40 per cent of which took a fatal course Auricular, atrio-ventricular and ventricular types were recorded If they occurred during an infection, of which pneumonia, tonsillitis and gastro-enteritis are mentioned, the extrasystoles sometimes disappeared when the infection had subsided Anatomically, gross pathological lesions were found in four horses In only one case were extrasystoles encountered in a healthy animal In the horse extrasystoles are much rarer than disturbances of atrio-ventricular conduction which were four times as frequent and were often found in otherwise healthy and strong animals Auricular fibrillation has been reported by several authors (Lewis, Norr, Roos)

Extrasystoles in only One Auricle

Extrasystoles confined to only one auricle have been reported in experimental conditions in which such premature beats were induced by induction shocks in an auricle after inter-auricular conduction had been abolished (Scherf and Siedek)

Fig 183 provides an example of such an observation made on a dog Both vagi had been severed and, as the resulting sinus tachycardia made the study of auricular activity impossible, complete A-V block was produced by clamping the bundle of His After the sinus node had been separated from the right auricle by means of small ligatures, applied between the A-V border and the angle between the superior vena cava and the right auricular appendage, inter-auricular block was observed The right auricle beat at a rate of 111 per minute (cycle length 0 54 second), the left, independently from the right, at 120 per minute (cycle length 0·50 second) An extrasystole elicited in the right auricle by an induction shock was not conducted to the left auricle The post-extrasystolic interval equalled the spontaneous right-auricular cycle length, which indicates that the site of origin of the extrasystole was at or near the site of the spontaneous impulse formation activating the

right auricle In these experiments, extrasystoles precipitated from the left auricle remained confined to this chamber, the post-extrasystolic interval being slightly longer than the spontaneous left-auricular cycle length, but not being compensatory. Auricular flutter confined to one auricle could also be produced in this series of experiments.

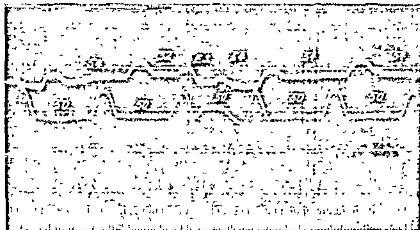


FIG 183 —From an experiment on a dog Tracings from above downward

auricle is not transmitted to the left auricle From Scherf and Siedek. *Z. Klin Med*

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CHAPTER X

THE LOCALIZATION OF THE SITE OF ORIGIN OF EXTRASYSTOLES

INTRODUCTORY REMARKS

To a certain degree localization of the site of origin of extrasystoles became possible in the pre-electrocardiographic era at an early stage of the work on extrasystolic arrhythmias. The analysis of arterial and venous pulse tracings and mechanical cardiograms made possible the distinction between extrasystoles arising in the ventricle, auricle, A-V node and S-A node With the advent of electrocardiography this work was, on the whole, confirmed, though in regard to some details previous conceptions were demonstrated to be based on fallacious interpretation of mechanical records and errors could be rectified The misinterpretation of atrio-ventricular extrasystoles as ventricular extrasystoles with retrograde conduction to the auricles may be cited as an instance (*see* section on " Atrio-Ventricular Extrasystoles ", p 168) But electrocardiography was expected to achieve far more than this· accurate localization of the site of origin of extrasystoles, that is, in right or left auricle or ventricle, and even accurate delimitation of the area within an auricle or ventricle was hoped for. In spite of much work and thought spent on this problem progress was disappointingly slow, results contradictory and even now this aspect of ectopic arrhythmias is far from solved

Up to quite recently it could justifiably be said that determination of the site of origin of extrasystoles had only an academic, if any, importance and that such studies were devoid of any general physiological or practical clinical value. That this view is no longer tenable will become apparent later in this chapter

VENTRICULAR EXTRASYSTOLES

The various stages in the development of our ideas about the site of origin of ventricular extrasystoles can conveniently, if arbitrarily, be divided into four periods: the first, from the investigations of Kraus and Nicolai starting in 1907 up to those of Rothberger and Winterberg in 1913 and of Lewis in 1916, the second, from 1913 to 1930 when the obser-

First Period, 1907–1913

established with complete certainty (" welches wir völlig sichergestellt haben ") The differences in the electrocardiogram were most pronounced if the heart was stimulated apically as far

to the left as possible and basally as far to the right as possible (Nicolai and Rehfisch, 1908). It is an instructive lesson, certainly of more than historical interest, that this "complete certainty" had to be partially questioned by the authors themselves as soon as the following year (Kraus and Nicolai, 1908) One year later Nicolai (1909) admitted that it was only possible to determine experimentally whether the abnormal contraction started in the right or left ventricle, something he considered akin to hemisystole, and in their monograph on the electrocardiogram Kraus and Nicolai, in 1910, gave up the idea of hemisystole altogether For Hering (1910) had concluded from his investigations that the direction of the initial deflection of extrasystoles depended on whether they were elicited from apex or base, and not whether they originated in the right or left ventricle; he used lead 1.

Nicolai (1909) and Kraus and Nicolai (1910) distinguished three different types of extrasystoles type A, originating in the apical portion, type B, arising in the basal parts, and type C, a central type, originating in an intermediate zone. In a lead from the right auricle and the left apex the initial deflections of type A were directed downwards, of B, upwards. To a certain extent the types A and B could, according to Kraus and Nicolai, also be ascribed to the left and right ventricle respectively This was supposed to be only accidental (p 164) and due to the fact that the anterior basal portion was predominantly formed by the right, and the apical by the left ventricle In a later section of the same book (p. 302/3),

the other hand, definitely expressed himself in favour of the former, and rejected the latter alternative He found that in lead 1 extrasystoles from the base and the apex of the right ventricle were directed upwards and those from the left apex in the opposite direction Results with lead 3 were inconclusive In later experiments (1910) he included for the first time the posterior aspect of the heart in such investigations and, using lead 2, arrived at the same interpretation

Rothberger and Winterberg (1910) examined the shape in the electrocardiogram of extrasystoles elicited mechanically in dogs, using an ano-oesophageal lead which closely corresponds to lead 3 In precipitating extrasystoles along a line running from the anterior border of the right auricular appendage to the apex the deflections were upright when precipitated from the first three points, all belonging to the right ventricle, and downward in the case of apical extrasystoles The direction changed as the line, along which the points of stimulation were situated, crossed the coronary sulcus Rothberger and Winterberg also showed that from an intermediate zone extrasystoles could be elicited which had an almost normal form in the electrocardiogram. The explanation, based on the view of Eppinger and Rothberger (1909) that the normal electrocardiogram is the resultant of two "antagonistic" forces, was that an artificial stimulus, so placed that it activates the ventricles in the *same succession as the normal impulse, yields an electrocardiogram which resembles* that of normal beats. Similar views about the origin of the normal electrocardiogram were expressed by Nicolai and Rehfisch (1908) and Selenin (1911). They are considered to deserve a brief reference as they anticipate by a considerable number of years the conception of the dual nature of the normal electrocardiogram which was later stressed by Lewis in 1916.

The main criticism of these earlier investigations is that the importance of the lead used for recording the action currents was not appreciated This is the more noteworthy as Einthoven fully realized this as early as 1908. He stated that, regarding the site of origin of extrasystoles, lead 1 distinguishes between right and left half of the heart, and lead 3 between apical and basal portions. Upward directed deflections in lead 1 indicated origin in the right, downward ones in the left half of the heart; upward and downward directed deflections in lead 3 were interpreted as signifying basal and apical origin respectively.

Second Period, 1913–1930

With the re-investigation on a large scale of this subject by Rothberger and Winterberg in 1913 work on this problem entered a new phase—the second part of our arbitrary division. In experiments on dogs extrasystoles were elicited from many points of the exposed heart and their shape in the electrocardiogram studied, lead 1 and the ano-oesophageal lead being recorded in immediate succession The main results regarding the direction of the initial ventricular deflections were:

1. Extrasystoles from the anterior surface of the left ventricle, near auricular appendage at the base· downward in lead 1, mainly upward in ano-oesophageal (a–o) lead

2 Extr asystoles elicited from a line starting at the left auricular appendage and running across the heart at equal distance from the apex upright throughout in a-o lead, in lead 1 changing from downward to upright at about a point where the above line crossed the coronary ul cus

3 Extrasystoles precipitated from a line running from the left auricular appendage to apex· downward throughout in lead 1; in a-o lead at first upright, but the height of the deflection decreased and an S wave of gradually increasing depth developed as the point of stimulation approached the apex, the direction of the T waves also became gradually reversed and from the apex typical " left " extrasystoles were obtained, that is, the initial deflections being directed downward, followed by high upright T waves.

4 Extrasystoles from the posterior surface usually the initial deflections were directed downward in both leads, but on crossing the interventricular sulcus from the left auricular appendage in the direction of the right ventricle they became upright in lead 1 The degree of rotation of the heart around its longitudinal axis was found to be of paramount importance

5 Extrasystoles from the right ventricle, precipitated from a line running from the middle of the right cardiac border to the apex and left border· upright in lead 1 as far as the coronary sulcus, thence smaller deflections until they became directed downward from points of the left cardiac border In the a-o lead transition also occurred at the coronary sulcus and it was noted that " basal " extrasystoles, (that is upward), were obtained from an area near the apex

These extensive investigations showed that the direction in the electrocardiogram of the initial deflections of ventricular extrasystoles could not unreservedly be assumed to indicate whether they originated, either in the right or the left ventricle, or in the basal or apical portion of a ventricle It is true that, regarding lead 1, the dividing line on the anterior surface between " right " and " left " ventricular extrasystoles ran along the coronary sulcus, but this was the case only in the more cranial portion More caudally, the line deviated to the left so that extrasystoles from the right portion of the apex of the left ventricle yielded " right " shapes. On the posterior surface the dividing line coincided more closely with the interventricular sulcus, particularly in its basal portions, but the degree of rotation of the heart had a decisive influence on the electrocardiographic appearance of the extrasystoles Regarding the a-o lead, no sharp dividing line between " right " and " left " or "apical " and " basal " extrasystoles was found on the anterior surface and an extensive zone yielded atypical complexes, extrasystoles from the posterior surface showed, in this lead, " left " (that is, downward directed) initial deflections except for a part at the base of the right ventricle, in which they had the opposite direction

The conclusion of Rothberger and Winterberg was that the appearance in the electrocardiogram of ventricular extrasystoles did not depend on the relation of the stimulated point, either to right or left ventricle, or to the distance from the midline, but probably depended on which muscular portions were first activated from the stimulated area Based on Nicolai's views about the distinction between spread of excitation through muscle and

that through the specialized conduction system Rothberger and Winterberg thought that the location of the stimulated point in relation to the point of the specialized system, whence the further spread of the excitation took place, was the factor decisive for the appearance in the electrocardiogram of the forced beats.

Lewis, whose views on the subject were to determine for many years the conceptions about the site of origin of extrasystoles, arrived at the same conclusions. In experiments on dogs (1916) he stimulated numerous (fourteen) points on the anterior surface of the right and left ventricle and, using an axial lead (lead 2), found the main initial deflection directed upward in extrasystoles elicited from the right, and downward in those from the left ventricle. No two stimulated points yielded identical deflections, but the nearer the points the closer was the resemblance in the record. On crossing the descending branch of the left coronary artery the type of complex in the electrocardiogram changed abruptly. This was attributed to the change in the side of the Purkinje network through which the impulse spread. By stimulation of a point immediately to the left of the coronary sulcus intermediate forms were recorded, closely resembling the complexes of normal beats. This observation, confirming that of Rothberger and Winterberg (1910), was explained by assuming that the excitation wave of the ventricular extrasystole spread through the Purkinje network of both the adjacent ventricles in a fashion similar to that of supraventricular beats. The study of such extrasystoles, arising near a septum, has recently attracted special interest (*see* below).

Applying these experimental observations, in which lead 2 was used (Lewis, 1925a), to the interpretation of human curves Lewis considered extrasystoles with upright initial deflections in lead 2 as arising in the right ventricle, those with a downward one as left ventricular in origin. The examples reproduced by him (Lewis, 1925b) indicate that downward initial deflections in lead 1 and upright ones in lead 3 were considered to indicate right ventricular origin, while downward complexes in all three leads in an instance of left ventricular extrasystoles were considered "atypical"; left ventricular extrasystoles were expected to yield upright deflections in lead 1 and downward ones in lead 3. Although Lewis himself pointed out, at the time, that it was impossible to localize spontaneous extrasystoles more than approximately and warned against applying to human records findings obtained in the dog heart, the above interpretation went unchallenged for many years. For Lewis's reading seemed to accord well with the electrocardiographic features of other conditions producing a predominantly left or right ventricular effect. Regarding the former, left ventricular preponderance in cases of hypertension or aortic valvular disease, and what was then believed to be right bundle branch block (old terminology) may be cited as instances: in these conditions, too, the main initial deflections were usually directed upwards in lead 1 and downward in lead 3. Similarly, predominating right ventricular effects were recorded as right ventricular preponderance in cases of mitral stenosis or chronic *cor pulmonale*, or in cases of what was then thought to be left bundle branch block (old terminology): such tracings showed the main initial deflections directed downward in lead 1 and upward in lead 3; the right ventricular origin of extrasystoles displaying such features seemed thus hardly questionable. It will be shown below, however, (p. 386), that all these interpretations had subsequently to be reconsidered.

Another line of approach to this problem was provided by *investigating the shape in the electrocardiogram of ectopic beats elicited in man* when the heart had become accessible for such studies. Considerable sources of error are present in such investigations as, if the heart was not exposed at operation, accurate localization of the stimulated point is not possible, and if the exposed heart was used, the very fact of exposure is likely to have influenced the

heart itself has to be excluded. With these reservations the most important papers on the subject may be briefly reviewed

In a patient, Hoffmann (1913) stimulated mechanically the heart which, after rib resection, was covered only by soft tissues and found that the initial ventricular deflections of the forced beats were directed downward in lead 1 and upward in lead 3, whatever the place of the mechanical stimulation was The published data are inadequate for any detailed analysis

A similar study was carried out in 1927 by Oppenheimer and Stewart in a man of sixty with marked scoliosis with its convexity to the left, in whom the lateral portions of the second to the eighth left ribs had been resected for empyema Auricular and forcible ventricular contractions were visible through the chest wall and helpful regarding the location of the mechanical stimuli (strokes with a percussion hammer) The presence of bradycardia due to complete A-V block facilitated effective stimulation Eight points were selected, four as much as possible to the left and four along the left sternal border as near as possible to the midline. If a point believed by the investigators to belong to the right ventricle was stimulated, the initial deflections of the forced beats were directed upward in lead 3; opposite direction was found in extrasystoles elicited from areas believed to be situated in the left ventricle It is, however, noteworthy that the small deflections in lead 1, hardly referred to by Oppenheimer and Stewart, were always directed downward, which, according to present views, tends to indicate left ventricular origin This possibility, also considered by the authors of the paper, became important in connexion with the subsequent work of Barker, Macleod and Alexander, referred to below. Oppenheimer and Stewart's tracings also show that, in lead 3, stimulation of points lying closer to the base yielded upright deflections, those situated near the apex, downward excursions, these results are in agreement with Einthoven's conceptions, mentioned above Apart from the inaccuracy of the location of the stimulated points, the main doubts about the validity of the results arise from the abnormal position of the heart and from the possibility of a pathological condition of the myocardium and/or conducting system, made probable by the presence of complete A-V block

A similar observation made by Fossier (1928) on a man of thirty-nine with congenital

point 5 being far to the right and 6 as far left as possible The conclusions were that premature contractions, the initial deflections of which were upright in leads 2 and 3, originate from the basal portions, while the opposite direction denotes apical origin

Third Period, 1930–1940

These investigations in man did not arouse much interest until Barker, Macleod and Alexander published in 1930 their observations on the results of artificial extrasystoles,

cardium 6 × 4 cm. Subsequent necropsy showed the heart to have been essentially normal. In all curves of forced beats from the right ventricle the initial deflections were upright in lead 1, they were downward in extrasystoles from the left ventricle It was thought that the direction of the deflections depended on whether the Purkinje system of the right or of the

leads 2 and 3 (particularly 2) signified the level of the focus of origin with reference to the long axis of the body These views are remarkably similar to those put forward by Einthoven more than twenty years earlier.

To a certain extent these results are also in accordance with those obtained experimentally by Rothberger and Winterberg (1913) They can also be reconciled with those of Fossier, after a slight re-interpretation of this author's findings, and with those of Oppenheimer and Stewart, if their curves are considered to have been obtained from the left ventricle which is very possible (*see* above)

The main importance of the study of Barker, Macleod and Alexander lay in the fact that their discordant curves were not in agreement with the views then held generally. (The term discordant signifies opposite direction of the main deflections in leads 1 and 3, whereas identical direction of these deflections is termed concordant.) If discordant curves with upright deflections in lead 1 were yielded by right ventricular extrasystoles, the conclusion became inevitable that these features, up to then considered to be a left ventricular effect, actually were right ventricular ones. A similar reversion of interpretation applied to discordant curves with downward deflections in lead 1, and such tracings had now to be assumed to be left ventricular effects The findings of Barker and collaborators had therefore a significance far exceeding that of localization of the focus of origin of extrasystoles They led to a re-interpretation of the curves obtained in cases of bundle branch block and to a new explanation of those indicating right or left ventricular preponderance.

The inference regarding bundle branch block was that, if discordant curves with initial deflections directed upward in lead 1—the common type—were a right ventricular effect, bundle branch block curves of this kind indicate left bundle branch block, and those with downward directed deflections in lead 1, right bundle branch block—a reversion of the terminology generally accepted up to that time. This view was supported by Wilson, Macleod and Barker By means of semidirect leads from the surface of the dog's heart with bundle branch block and by serial precordial leads in subjects with bundle branch block, tracings were obtained which demonstrated that the "common type" of bundle branch block was a block of the *left* bundle branch As far as preponderance curves were concerned, it could not be questioned that in cases of hypertrophy of the left ventricle discordant curves with upright deflections in lead 1 were encountered in the majority of cases If such tracings had now to be considered as representing right ventricular effects, a new explanation for their occurrence in cases of left ventricular hypertrophy had to be sought. This consisted in the assumption that, in such cases, the spread of the excitation wave through the hypertrophied left ventricular wall resulted in a delay of the spread of impulse, with the result that the first portion of the initial ventricular deflections was determined by the right ventricle, displacement of the septum to the right and rotation of the heart were further factors responsible for the electrocardiographic features

This reversal of terminology regarding focus of origin of extrasystoles as well as that of bundle branch block has become generally accepted Objections were first raised by Rothberger (1933) who compared the shape of extrasystoles obtained in experiments by him with Winterberg (1913) with those in which one main bundle branch and all divisions except one of the other branch were cut (Rothberger and Winterberg, 1917) and concluded that the old terminology was correct He also stressed the difference in structure and position of the heart of the dog compared with the human, and the necessity of very thorough and expert [illegible]

[illegible]

and collaborators as a result of stimulation of various points of the exposed human heart were confirmed in similar cases by several authors (Marvin and Oughterson, 1932, electrical

stimulation of one point each of the anterior and posterior surfaces of the heart in a man of thirty-eight with right-sided empyema and pericarditis, Padilla and Cossio, 1932, by mechanical puncture of the right ventricle in a patient with Hodgkins disease; Vander Veer, 1933, mechanical stimulation of the right ventricle in a boy of eleven operated for Pick's syndrome; Lundy and Bacon, 1933, in a boy of four with purulent pericardial effusion, electrical stimulation of two points on the left ventricle, one near its base on the lateral posterior border, the other near the apex, both yielded discordant tracings, from the first point the deflection being upright in lead 1 and downward in lead 3, from the apical point the reverse)

The revised terminology was also supported by experimental work amongst which the extensive investigations by Storm (1936) on Javanese monkeys (*macaca irus*) should be mentioned in some detail, since Storm's monograph is an important contribution and not easily accessible. Storm points out that much of the work on this subject had been unsatisfactory or at least not entirely convincing for the following reasons

1. An insufficient number of leads were taken or the type of lead employed was not indicated;

2. Leads were used in experimental work which were not comparable to those used in clinical practice (for example, ano-oesophageal or direct leads);

3 The three limb leads were not recorded simultaneously,

4 The heart was in an abnormal position (for instance, because of the thorax having been opened or pathological conditions being present in the surrounding structures);

5. The contact between the heart and surrounding structures was inadequate or variable (for instance, resulting from opening the thorax),

6 The stimulus was not sufficiently localized,

7 An insufficient number of points were stimulated,

8 The stimulus was applied on the surface whereas deeper layers should have been used,

9 The applicability to conditions in man of results obtained in some of the experimental work is doubtful,

10. The heart was in a pathological condition.

Storm took great pains to avoid these pitfalls In twelve monkeys he stimulated by means of induction shocks eighty-six different points on the anterior and posterior surfaces of the heart, the thorax being closed and respiration being spontaneous The three standard leads were recorded simultaneously His results were as follows

1 The initial deflections in lead 1 of all premature beats originating in the right ventricle were directed upwards, of those originating in the left ventricle, downwards,

2 The initial deflections in leads 2 and 3 of all premature beats originating from the base were directed upwards, of those originating in the apex, downwards, irrespective of whether they were elicited from the right or the left ventricle,

3 As the point of stimulation was moved from the apex towards the base an intermediate zone was found in which the initial deflections changed from a downward to an upright direction,

4 Generally the ectopic beats showed a pure diphasic form, consisting of an initial and final deflection, the latter being in an opposite direction to the former, but beats elicited from the region of the interventricular groove showed polyphasic features often having some resemblance to complexes of normal beats,

5. Ectopic beats originating in corresponding points of the anterior and posterior surface of the heart showed, as a rule, similar features in the electrocardiogram.

These conclusions support the revision of Lewis's terminology and are in accordance with the older work of Einthoven.

In the light of recent developments Storm's statement is of particular interest that his results conflict with the opinion of Lewis that, in the case of ventricular premature beats, activation of the ventricular wall "just as in the case of the normal contraction, always proceeds from within outwards and in the same way". (Storm, p. 179.) In Storm's opinion Lewis's observations are better explained on the basis of the old interference theory, that is, by assuming that negativity of the ventricular wall starts at the point of stimulation irrespective of whether that negativity had travelled from within outwards or in the reverse direction By way of comment we should like to point out that Storm's account of Lewis's work seems incomplete, since Lewis fully considered direct spread through muscle (*see* section on "Spread", p 371)

By a different ingenious method, designed by Battro, Braun-Menendez and Orias for investigating patients with bundle branch block, Castex, Battro and González (1941) obtained results which were in accordance with Barker and collaborators, as far as lead I is concerned The method is based on detecting and analysing the asynchronism between the contraction of the two ventricles by simultaneously recording electrocardiogram, phonocardiogram and central arterial or venous pulse. Out of twenty-three cases of spontaneous extrasystoles examined in this way, ten showed downward and thirteen upright deflections in lead 1, and by the above method it was found that those with a downward deflection arose in the left ventricle, whereas upright deflection was associated with origin in the right ventricle

Other investigations, while essentially confirming the view of Barker and collaborators, lead to the recognition of various complicating factors

The patient investigated by Prinzmetal, Oppenheimer and Dack (1937), a man of thirty-eight, with constrictive pericarditis and a right-sided hydrothorax, had right axis deviation in the electrocardiogram During the second of two operations for partial pericardiectomy extrasystoles elicited from the left ventricle, about 3 cm to the left of the septum, yielded small upright deflections in lead 1 and upright deflections in lead 3, the two leads being simultaneously recorded Subsequently, some time after operation, extrasystoles were precipitated through the chest wall by tapping and, since at operation the right ventricle had been noticed to form nearly the whole area in contact with the anterior chest wall, it seems reasonable to assume that such extrasystoles originated in the right ventricle In three of the four stimulated points the extrasystoles gave deflections which were directed downwards in lead 1 and upwards in lead 3; the opposite was found only in the fourth point situated furthest caudad These findings do not conform with the new terminology. Prinzmetal and his collaborators attribute this discrepancy to the presence of right axis deviation and claim that the new nomenclature seems applicable only if the direction of the electrical axis is normal or if there is left axis deviation Similar discrepancies, due to the same factor, seem to have been present in the case of Lundy and Bacon (*see* above) and possibly in that of Oppenheimer and Stewart (*see* above) The fact that at the first experiment the heart was exposed, whereas at the subsequent one it was covered may also have contributed to the different results obtained by Prinzmetal, Oppenheimer and Dack

By eliciting extrasystoles from the points used by Barker and collaborators, Kountz, Prinzmetal, Pearson and Koenig (1935) confirmed in human hearts revived immediately after death the findings of Wilson and collaborators regarding bundle branch block tracings and, with unimportant exceptions, those of Barker and collaborators regarding extrasystoles. By shifting the heart they also confirmed Barker's prediction that what was right axis deviation in the old terminology actually is left axis deviation and vice versa. In cases in which there was right axis deviation (old terminology) because of an abnormal position of the heart or of failure of a portion of the left heart to revive, the tracings of bundle branch block may be reversed. The last observation, in accordance with those of Prinzmetal, Oppenheimer and Dack on the living subject (discussed above), emphasizes the importance

of the direction of the electrical axis in such determinations. Rotation of the heart was also found to be of importance

Further investigations of Kountz, Prinzmetal and Smith (1935a) were directed to clarify the differences in observations on the heart of dogs and of human beings By accurately placing dogs' hearts into the human thorax these authors confirmed the findings of Barker and collaborators regarding bundle branch block and extrasystoles Some differences were found to be due to the different configuration of the chest in the dog as compared with that in man, since, in the dog, the thorax is deeper and on opening the chest the heart falls back into the posterior mediastinum This accounts for certain changes in the experimental findings on these two species, not only because of differences in the position of the heart, but also as a result of altered contact between the heart and surrounding structures In monkeys, whose chest resembles more the human one than that of dogs, the above results were confirmed (Kountz, Prinzmetal and Smith, 1935b).

[illegible]

authors elicited extrasystoles from many points in close proximity to one another. Such lines of transition were found not to conform with any anatomical boundaries on the surface of the two ventricles Localization of extrasystoles regarding right or left ventricle was found not possible from lead 1, and the configuration in lead 3 depended essentially on whether the anterior or posterior surface of the heart was stimulated No diagnostic significance was found to be attached to concordancy or discordancy of the tracings and such terms were considered superfluous With rotation of the heart around its long axis the lines of transition remained practically unaltered in relation to the long axis of the body (that is, the lines shifted correspondingly on the surface of the heart), whereas with other types of change of position (moving apex to right or left without rotation, or displacement of the apex sternad or vertebrad) the lines of transition remained unchanged in relation to the surface of the heart and shifted correspondingly relative to the long axis of the body. Another point of interest is that such lines of transition could be modified by a shunt between the heart and the axilla or by interposing an insulator between the posterior surface of the heart and the muscles, illustrating the importance of the structure of the surrounding media Some of these results had previously been obtained in cats by Abramson and Weinstein (1936)

Katz and Ackerman (1932) had gone so far as to declare impossible any localization of [illegible]

to go too far, for even if the shape of the complexes in the tracings is materially changed by an altered position of the heart, the direction of the main deflections often remains the same Moreover, Foster (1935) pointed out that the degree of change of position found necessary experimentally to produce such electrocardiographic variations in bundle branch block was often excessive. Further objections to applying, to the localization of the focus of origin of extrasystoles, interpretation of bundle branch block tracings will be discussed below. To [illegible]

and superficial sino-spiral muscles) (Robb, Robb and Hiss, 1935) was as unsuccessful as a similar endeavour of the same school of workers to explain on the same basis the mode of spread of the excitation through the myocardium (*see* section on "Spread", p 376)

The stage reached at that time, aptly surveyed by Moia and Batlle (1937), can be *summarized* thus: On the whole, most of the work was in accordance with Rothberger and Winterberg's results obtained in dogs in 1913. Contrary to Lewis's view, with the heart in a normal position extrasystoles originating in the right ventricle generally yield upright deflections in lead 1, and left ventricular extrasystoles, downward deflections in lead 1; in both instances the tracings can be concordant or discordant, according to the situation of the stimulated point The reversal of the old terminology, resulting from the work of Barker and collaborators, had become generally accepted: discordant curves with upright initial deflections in lead 1 and downward ones in lead 3, previously considered to denote a left ventricular effect, actually were right ventricular ones and vice versa, and this reversal was applied to the location of the focus of origin of extrasystoles and to the side of the lesion in bundle branch block. Lead 3 permits only differentiation between basal or apical origin Therefore extrasystoles originating in either ventricle may show concordant or discordant tracings The importance of the position of the heart and of the structure of surrounding tissues was realized. But the picture as a whole was still confused and confusing In particular, the meaning of discordant and concordant tracings was obscure, some exceptions of experimental results regarding the occurrence of "left" or "right" ventricular extrasystoles elicited from portions of the contralateral ventricle could not be satisfactorily explained, and the applicability of findings obtained in cases of bundle branch block to those of extrasystoles and vice versa was not entirely clarified.

Fourth Period, Since 1940

At this stage the extensive investigations of Nahum, Hoff and collaborators started which we took as marking the beginning of our fourth period. This work, if confirmed, would not only throw light on some of the above questions, but also, as will be shown, would re-open some allied problems of cardiac physiology which have a bearing on the principles of the genesis and interpretation of electrocardiograms. While this work is of sufficient importance to warrant a detailed discussion in this monograph, it should be emphasized at the start that, at present, it has not been confirmed and that the views of Nahum, Hoff and collaborators are not supported by the results of vectoranalysis and vectorcardiography. These contradictions are pointed out later in this chapter (p. 397), after the investigations of this school of workers have been discussed

These studies started by a re-investigation of the influence of the right and left ventricle on the electrocardiogram (Hoff, Nahum and Kisch, 1941). By means of surface application of a M/10 or M/5 solution of KCl these workers claimed to have eliminated in experiments on dogs the surface electrical activity of certain parts of the heart and, in this way, to be able to obtain "dextro- and laevocardiograms". By warming or cooling the right or left ventricle, and by eliciting extrasystoles from symmetrically located points equidistant to the right or left from the septum, they obtained asynchronism in the contraction between the right and left ventricle and concluded that the upstroke of the R wave is formed by the upstroke of the dextrocardiogram whereas the downstroke is due to the laevocardiogram. Extrasystoles precipitated from the left ventricle yielded downward deflections in all three conventional leads, provided that the point of stimulation was sufficiently removed from the septum for the excitation to activate the greater part of the left ventricle before reaching the right one. Extrasystoles from the right ventricle yielded upright initial deflections in the three leads (Nahum, Hoff and Kaufman, 1941a), with similar qualifications regarding activa- [illegible]

[illegible]

sumed to be the source of action potentials, and it was concluded that the dextrocardiogram in

lead 1 must be derived from the posterior surface of the right ventricle (called posterior dextrocardiogram) and, equally, the laevocardiogram in lead 3 must have been produced by the posterior surface of the left ventricle (posterior laevocardiogram) If, on the other hand, the *posterior* surface of *both* ventricles was treated with a KCl pledget, a laevocardiogram [illegible] laevo-

interior

dextro-

of the

interior

dextrocardiogram and the posterior laevocardiogram Lead 2 was said to record from the whole heart (Hoff, Nahum and Kaufman, 1941)

We cannot accept these interpretations as it is certain that the surface areas of the heart are not the only portions which contribute to the electrocardiogram It is the same electrical event which we record in all three leads at any given moment

Nahum, Hoff *et al* concluded further that extrasystoles arising in the anterior or posterior septal regions, and activating the anterior or posterior surfaces respectively of both ventricles in advance of the opposite surface, should have a predictable configuration in the electrocardiogram For example, an extrasystole originating from or near the anterior septum should reveal *activation of the anterior surface of the left ventricle in advance of its* posterior surface (that is, anterior laevocardiogram, downward deflection in lead 1) and also activation of the *anterior* surface of the *right* ventricle in advance of its posterior surface (that is, anterior dextrocardiogram, upright deflection in lead 3) Similarly, extrasystoles arising from or near the posterior septum, and activating the posterior surfaces of both ventricles in advance of their anterior ones, should yield upright deflection in lead 1 (posterior dextrocardic [illegible]

These predictions [illegible]

Kaufman, 1941b) [illegible]

anterior surface of both ventricles resemble those of " right axis deviation " and right bundle branch block (new terminology), those resulting from the preceding activation of the posterior surfaces of both ventricles, " left axis deviation " and left bundle branch block All these tracings were, of course, discordant Similarly, concordant records with upright deflections in leads 1 and 3 were interpreted as indicating that the major portion of the right ventricle is activated before the left one, and concordant tracings with downward deflections in leads 1 and 3, preceding activation of the major portion of the left ventricle before the right

A more detailed investigation of the electrocardiographic features of extrasystoles elicited in various parts of the two ventricles showed that right ventricular ones showed downward deflections in certain leads (except those from an area equidistant from all points along the septum, termed centre of the ventricle, which yielded upright deflections in all three leads) Those downward deflections were shown to arise from excitation of the contralateral—left—ventricle Conversely, left ventricular extrasystoles yielded downward deflections in all leads only if they originated from a restricted area in the " centre " of the left ventricle, upward deflections produced in certain leads by left ventricular extrasystoles arising in other portions of the left ventricle were shown to result from stimulation of the right—contralateral—ventricle (*see also* above in this chapter, p 390) (Nahum, Hoff and Kaufman, 1942)

[illegible]

cardiogram had previously been reported by Marcu (1936), Loukomski and Guinodman (1937) and Van Bogaert (1937), but had not attracted much attention Hoff and Nahum

(1943) confirmed this and realized the great importance which this observation has in regard to the interpretation of the genesis of the various deflections in the electrocardiogram (*see* below) They also found two areas in the heart (one in the anterior left and the other in the posterior right ventricle) where epi- and endocardial extrasystoles showed different shapes in the electrocardiogram and here again they explained such differences as being due to excitation of the contralateral ventricle.

It was then considered possible that chest leads might be more sensitive to detect differences in endo- and epicardial extrasystoles. Epicardial extrasystoles and their exact endocardial counterparts were therefore studied in seven dogs by a transthoracic lead, lead IVR, IVF and unipolar (Wilson) lead V. The position of the stimulating electrodes was carefully arranged in some experiments they were perfectly centred in line between the transthoracic leads, or placed directly beneath the exploring chest electrode; in others they were deliberately placed out of alignment: either the exploring chest electrode remained in position over the right or left apex and the position of the stimulating electrodes was altered, or the precordial electrode was shifted whilst the stimulating electrodes remained in position With the stimulating electrodes in line with the transthoracic lead, or immediately beneath the exploring chest electrode, no differences between endo- and epicardial extrasystoles were found, both showed downward (QS) deflections, that is negativity beneath the exploring chest electrode When the stimulating electrodes were not in alignment with the transthoracic lead, or not beneath the exploring chest electrode, various kinds of differences between endo- and epicardial extrasystoles were recorded No potentials which must accompany the outward passage of an impulse from endocardium to epicardium were recorded. The optimum conditions in which such potentials could be revealed would be those in which the stimulating electrodes were directly in line with the transthoracic lead, or directly beneath the exploring chest electrode, and these were precisely the conditions in which no differences between endo- and epicardial extrasystoles were encountered (Nahum and Hoff, 1946)

This observation conflicts with that of Lewis (1922), which had been of such great importance for our views regarding the mechanism of origin of the deflections in the electrocardiogram. Using a transthoracic lead in experiments on dogs, Lewis stimulated the endocardial and immediately overlying epicardial surface of the right ventricle. With forced beats from the endocardium the deflections started with a small downward wave, whereas with epicardial extrasystoles the small first wave was directed upwards. From this observation Lewis developed his theory of " limited potential differences ". By this is meant that the ventricle should be considered to be composed of a great number of small units and that it is the direction of successive activation of such muscle units which governs the deflection in the electrocardiogram. Lewis expressly refuted the view that the position of the activated muscle relative to the rest of the ventricle influenced the electric record.

By this time, certain factors responsible for disagreement in the past had become apparent of which Nahum and Hoff considered three as the most important (Nahum and Hoff, 1945):

1. *Failure to provide for normal conduction from the heart to distant leads.* This factor tends to become operative in experiments on animals with widely opened thorax and on human beings with exposed hearts, as already stressed by Storm.

2. *Preoccupation with the site of origin to the neglect of the sequence of excitation of adjacent and distant regions of the heart.* The attempted interpretation of extrasystoles as arising in the right or the left ventricle failed to consider those ectopic beats which originated at or near a septum and thence spread simultaneously to adjacent portions of both ventricles before reaching the more distant parts of the ventricle in which they had arisen This factor accounts for some of the " exceptions " which were mentioned earlier in this chapter. Basing their classification on investigations discussed above (p. 390, Nahum, Hoff

and Kaufman, 1941a, Hoff, Nahum and Kaufman, 1941), Nahum and Hoff recognized four basic patterns which included concordant as well as discordant tracings, namely:

(1) right lateral, concordant, main initial deflection upward in all limb leads, from the base of the right ventricle to within a few mm of the septum at the apex,
(2) left lateral, concordant, main initial deflection downward in all limb leads, from the left lateral margin of the heart including the apex to within about 5 mm of the septum;
(3) anterior septal, discordant, main initial deflection downward in lead 1, upward in 3, from a zone not more than 0·5–2 cm of the apex,
(4) posterior septal, discordant, main initial deflection upward in lead 1, downward in 3, from a zone 0 5–1 cm wide extending from the apex (or a few mm. anterior to it) to the base

In all types the T waves were directed opposite to the direction of the main initial deflections. In terms of excitation of the various parts of the heart these four basic patterns were interpreted thus

(1) right lateral pattern anterior and posterior surface of the right ventricle activated in advance of the counterparts of the left ventricle, origin of extrasystole in the "centre" of the right ventricle (that is, equidistant from the septum);
(2) left lateral pattern· anterior and posterior surface of the left ventricle activated in advance of the counterparts of the right ventricle, origin of extrasystole in the "centre" of the left ventricle,
(3) anterior septal pattern anterior left ventricle excited in advance of posterior right, and anterior right ventricle excited in advance of posterior left ventricle, origin of extrasystole at or near the anterior septum,
(4) posterior septal pattern posterior surfaces of the two ventricles excited in advance of their anterior surfaces, origin of extrasystole at or near the posterior septum

(For the detailed reasoning, *see* the original paper)

3 *Inferences from experiments on bundle branch block regarding the site of origin of extrasystoles* Some of the difficulties created by such inferences became apparent in earlier parts of this chapter Barker and collaborators had pointed out that stimulation of all points on the right or the left ventricle does not necessarily yield complexes in the electrocardiogram which closely resemble in all leads those produced by cutting the bundle branch [illegible]

" This does not imply that the whole of the normally stimulated ventricle is necessarily activated in advance of the other." They [illegible]

[illegible]

Lewis, Wilson and their collaborators In the present context the relevant point of this theory is that in unipolar leads the direction of the deflections is entirely due to the direction of the spread of the excitation relative to the exploring electrode and that more distant parts of the heart contribute only to a small extent

This view cannot be reconciled with the observation of Nahum and Hoff, discussed

above, that extrasystoles from the epicardium and a point immediately subjacent on the endocardium are virtually indistinguishable in the electrocardiogram. On the contrary, these workers claim that excitation and recovery on the surface are the factors which determine the electrocardiogram. Moreover, it was found that "all experimental procedures which modify the several components of the normal ventricular complex of an electrocardiogram in a special way produce similar modifications in the same component of a ventricular extrasystole" The increase in height of the R wave by cooling the left or warming the right ventricle, applying equally to extrasystoles and normal complexes, and the identical mode of origin and significance of Q waves in ventricular extrasystoles and normal beats (Hoff, Nahum and Kaufman, 1942), may be quoted as two of several instances. (For others, *see* Nahum and Hoff, 1945, p. 548.)

This led Nahum and Hoff to the conception of the "zonal interference" theory according to which the electrocardiogram of unipolar leads is the result of only two opposing forces the excitation of a proximal region, that is at or near or facing the exploring electrode, producing a downward deflection, (negativity of the exploring electrode), and that of a distal region resulting in an upward deflection, the two zones being separated by an intermediate zone. These deflections are stated to be independent of the pathway by which the excitation arrives.

This conception was developed in regard to unipolar limb leads and the praecordial electrocardiogram of the dog

Findings regarding unipolar limb leads may be illustrated by lead VR, obtained by an exploring electrode on the right forelimb, which was paired with a central terminal from right and left forelimbs and left hind limb In order to delimit the proximal, distal and intermediate zones, several methods were employed. By momentarily applying positive or negative electrical potentials of low voltage to various parts of the heart, the areas from which downward or upright deflections were obtained were mapped out. The direction of the main initial deflection of extrasystoles, produced by break shocks, in various parts of the heart was charted and similarly the effect upon the S-T segment of localized surface injury from application of M/5 KCl solution or superficial cautery. These methods gave consistent results in delimiting a proximal zone, facing the electrode, and a distal zone, facing away from the electrode, which were separated by an intermediate zone. Extrasystoles originating in the proximal zone showed the main deflection directed downward (QS complex), those arising in the distal zone produced an upward deflection (R wave), those from the intermediate zone an rS or qRs complex. Similarly, elevation of the S-T segment as a result of local injury localized the site of injury in the proximal, depression of S-T in the distal zone Impressed negative potentials on the right ventricle caused a negative, on the left ventricle an upward deflection. By these methods the proximal, distal and intermediate zones were mapped out in detail for leads VR, VL and VF (Nahum, Chernoff and Kaufman, 1948a).

Similar investigations were carried out regarding the mode of origin of the T wave (Hoff and Nahum, 1948)

As already mentioned, this group of workers endeavoured to show that in each of the three unipolar limb leads a proximal, distal and intermediate zone, specific for each of these leads, could be delimited. Extrasystoles originating in the proximal zone were characterized in the particular lead by an initial downward, those from the distal zone by an upward deflection. These zones were, however, comparatively large. Delimitation of the site of origin within a smaller area was attempted by simultaneously recording two or three unipolar extremity leads. Since the proximal, distal and intermediate zones of these three leads overlap, such simultaneous recording would delimit the site of origin of extrasystoles within a far narrower area. This may be illustrated by Fig. 184, taken from Nahum, Chernoff and Kaufman, 1948b. For example, an extrasystole showing a downward initial deflection in

leads VR and VL and an upward deflection in lead VF can be assumed to originate in a zone which is proximal in leads VR and VL and distal in lead VF and therefore would be situated in the basal part of the anterior surface of the right ventricle (marked PPD in the diagram) In a similar way an extrasystole showing an upward deflection in leads VR and VL and a downward one in lead VF was assumed to have arisen in a zone which is distal

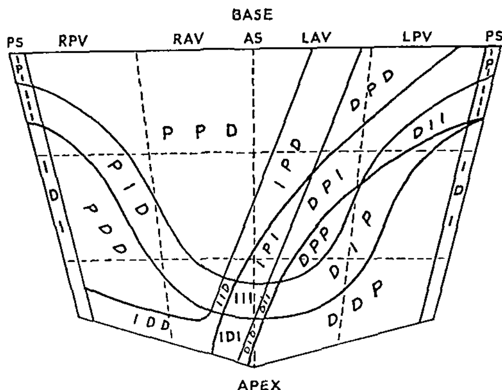


FIG 184.—Schematic drawing of ventricular surface of dog heart showing

in leads VR and VL and proximal in lead VF, which localizes its origin in the apical portion of the anterior surface and the apical and middle portions of the posterior surface of the left ventricle, designated DDP

This group of workers also applied their methods to a more detailed analysis of standard (bipolar) limb leads

An isoelectric interval in the record of a bipolar lead may be due to any one of three possibilities·

(1) negative potentials of equal magnitude at both extremities;

(2) positive potentials of equal magnitude at both extremities;

(3) zero potentials at both extremities (Nahum, Chernoff and Kaufman, 1948b)

By simultaneously recording one bipolar and two unipolar limb leads the authors considered possible

1. to determine which of the combinations of potentials of the two individual extremities resulted, in a bipolar limb lead, in an upward or downward deflection or an isoelectric interval, and

2 to delimit within a narrower area the site of origin of extrasystoles yielding upright *or downward deflections in lead 1 or 3 than had been possible by the limb leads alone.*

In the context of this book the second aspect is the more relevant.

In earlier investigations (Nahum, Hoff and Kaufman, 1941a; Hoff, Nahum and Kaufman, 1941, Nahum and Hoff, 1945), discussed above, these workers recognized four basic patterns of ventricular extrasystoles according to the direction of the deflection in the bipolar limb leads, each pattern indicating the site of origin within a comparatively large area of the heart By analysing the mechanism of these deflections in the limb leads into the simultaneously recorded deflections in each of the two component unipolar leads the authors attempted to delimit the area of depolarization—and in the case of extrasystoles this gives an indication of the site of their origin—within a considerably smaller portion of the heart Lead I was studied as a derivation from an analysis of simultaneously recorded leads VR and VL, lead 3 of leads VL and VF

This may be illustrated in respect of lead 1. From earlier investigations the same group of workers had concluded that, in this lead, an upright deflection resulted mainly from depolarization of the posterior right ventricle, and a downward deflection from that of the anterior left ventricle Further investigations with simultaneously recorded unipolar limb leads revealed that the greatest upward deflection occurred as a result of depolarization of the mid-third of the posterior right ventricle. The reason was found to be that extrasystoles precipitated from this area yielded opposite deflections in the unipolar leads VR and VL (downward in the former, upright in the latter), and since the right forelimb was initially negative relative to the left one, lead 1 showed a large upward deflection. Conversely, the largest downward deflections in lead I were found when the mid-third of the anterior left ventricle was depolarized, extrasystoles elicited in this area produced opposite deflections in leads VR and VL (upright in the former, downward in the latter), and since the right forelimb was initially positive relative to the left one, such extrasystoles yielded large downward deflections in lead I

The inclusion, in these studies, of those parts of the heart the depolarization of which did not manifest itself by an appreciable deflection in lead 1 made it possible to analyse which of the three possibilities, mentioned above, resulted in isoelectricity. Extrasystoles elicited from one of these portions, namely, the lower third of the posterior left ventricle, showed an interesting feature: during the first 0 04 second an isoelectric interval was recorded in lead 1, although the rapid downward deflection in lead 3 during that interval indicated that parts of the heart were being activated during that time. The explanation *for this isoelectric interval in lead 1 was revealed by leads VR and VL in* both of which the deflection, during that 0 04 second, was ascending with the same gradient: since at both forelimbs potentials of the same magnitude and of the same electrical sign developed at the same speed, no potential differences between the two forelimbs were recorded in lead 1.

In a similar way lead 3 was analysed from simultaneously recorded leads VF and VL with regard to regions of the heart, the depolarization of which yielded maximal, less than maximal and no deflections in this limb lead. In both leads 1 and 3 the effect upon the T wave of accelerating or decelerating repolarization by warming or cooling various portions of the heart was also investigated.

These extensive investigations seemed to their authors to be in agreement with their earlier findings that lead 1 records the algebraic summation of potentials derived mainly from depolarization of the posterior right and anterior left ventricles, whereas that of the anterior right and posterior left ventricles was not represented in this lead; that lead 3 records the algebraic summation of potentials derived mainly from depolarization of the anterior right and posterior left ventricles, whereas that of the anterior left and posterior right ventricles was not represented in this lead. By this method delimitation of the area of depolarization within a more specific and circumscribed area of the heart was claimed and a " basis for the presence or absence of electrical representation of the various regions of the heart " in leads 1 and 3 was thought to have been established

In a similar way proximal, distal and intermediate zones were mapped out for praecordial leads (Nahum and Hoff, 1948) The exploring chest electrode was placed either opposite the left apex on the left side of the chest, or the right apex on the right side of the chest CF, CR and CV leads were employed and the delimitation of the zones investigated by three methods:

(1) influence on the S-T segment of localized application of 0·1 M KCl solution,

(2) influence upon the T wave of local warming and cooling;

and

(3) the shape of extrasystoles elicited from various parts of the heart.

These three methods gave consistent results As far as extrasystoles are concerned, those precipitated in the proximal zone yielded simple QS deflections, those arising in the distant zone, R waves, and those elicited in the intermediate zone showed QRS patterns, with the R wave becoming more prominent as the point of stimulation approached the distal, and the S waves as it approached the proximal zone In all leads studied the " method of extrasystoles " permitted a more exact definition of the various zones than did the effect of warming or cooling or localized surface injury. The three leads employed yielded essentially the same information, but leads CR and CF were slightly superior to CV regarding sharpness of delimitation of the various zones " With each position of the chest electrode, the proximal zone always included at least the apex of the ventricle corresponding to the side of the chest lead selected, while the distal zone always included some portions of the base of the heart. In other words, the chest leads always included an element of base-apex interference " Figs. 185 and 186, taken from their paper, show the position, size and shape of the three zones

All such analyses are based on the " zonal interference theory " of this school of workers This conflicts with Lewis's theory of " limited potential differences " which, as further developed by Wilson and his collaborators, has been the universally accepted basis of the [illegible]

been confirmed so far On the contrary, Attyah found in dogs that electrical stimulation of the endocardial surface of the free wall of the right ventricle consistently yielded initial positivity on the superjacent epicardial electrode (which was paired with Wilson's central terminal) This is in accordance with the dipole theory and at variance with Nahum and Hoff's findings On the other hand, Durant and Oppenheimer, studying in dogs extrasystoles elicited mechanically, found a small area producing initial negativity in direct leads from the site of stimulation They also obtained a small point of initial negativity in spontaneous systoles, and found that the zonal interference theory best explained their experimental results which would be difficult to understand on the basis of the dipole theory

A more serious, fundamental objection to the zonal interference theory is the fact that it conflicts with the results of vectoranalysis and vectorcardiography. These methods have

shown that *all* parts of the heart contribute to the electrocardiogram at any moment in any lead They have also demonstrated that the degree of proximity of an electrode to a given region of the heart influences the contour of the record to a far smaller extent than previously assumed and have cast doubt on the possibility of identifying an " intrinsic " deflection as indicating the arrival of the excitation beneath the exploring electrode. Moreover, tracings obtained from diametrically opposite points of the chest yield deflections which are mirror images of one another. For further particulars of these investigations the reader is referred to the monographs of Duchosal and Sulzer, and of Grant and Estes

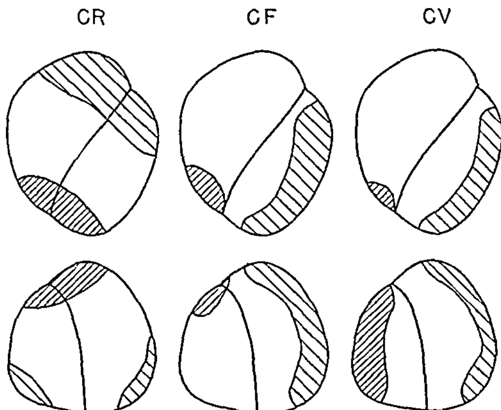


FIG 185 —Summary of the proximal and distal zones of the dog heart when the lead is taken with the exploring electrode placed over the right apex, CR, CF and CV leads *Above*, ventral surface of the heart, apex down, *below*, dorsal surface of the heart, apex up *Fine shading* proximal zones; *coarse shading*, distal zones For further explanation, see text From NAHUM and HOFF, 1948 *Amer J Physiol*

The relevant fact in the present context is that, because of these findings, grave doubts exist about the validity of the conclusions which Nahum, Hoff and their co-workers have drawn from their investigations, and in particular about that of the zonal interference theory. The outcome of further investigations has to be awaited before a definite opinion can be formed.

Oesophageal Leads

The use of oesophageal leads has not proved very helpful in the determination of the site of origin of ventricular extrasystoles (Brown, Spuhler, Wunsche, 1948) It is of interest that

the oesophageal pulsations (that is pulsations of auricle and ventricle transmitted to the oesophagus) were used for the analysis of extrasystoles as early as 1907 (Rautenberg)

Endocardial Leads

Of late, studies on intracavity potentials have supplemented these observations, but as

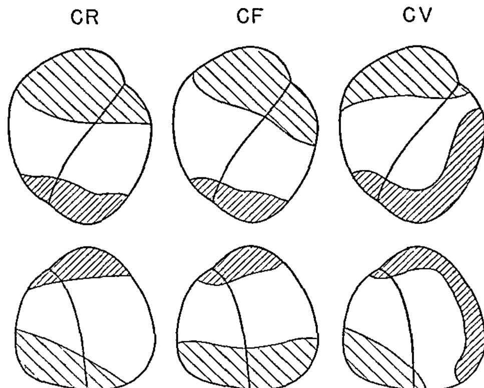


FIG 186.—Summary of proximal and distal zones of the heart when the lead is taken with the exploring electrode over the left apex *Fine shading*, proximal zones, *coarse shading*, distal zones For further explanation, see text From NAHUM and HOFF, 1948 *Amer J Physiol*

1947, Battro, 1948, Levine *et al*, 1949), and in dogs (Sodi Pallares *et al*), whereas left ventricular extrasystoles give RS deflections (Hecht, 1946, Battro and Bidoggia) The electroendocardiogram from the right ventricle of right ventricular extrasystoles resembles in its deep QS deflections those of left bundle branch block, and that of left ventricular extra-

as to the underlying mechanism. Apart from having been established as yet on a small number of cases the tracings reproduced in the few publications are not strictly comparable

because of technical reasons (for instance, wide exposure of the heart and the use of only one limb for the indifferent electrode, Sodi Pallares). With these reservations it may be said that most findings are in accordance with the dipole theory and Wilson's views based thereon, but the intracavity potentials recorded of extrasystoles would also be in accordance with the conception of Nahum and Hoff. In most observations made on man these refer to right ventricular extrasystoles, and there are good reasons for assuming that they were produced by the exploring intracavity electrode mainly from the point where it was in intermittent contact with the endocardial surface of the right ventricle (Levine *et al*) In this event, the intracardiac electrode being at the same time the (mechanically) stimulating and the recording electrode, the deep QS deflections, being obtained from the very site of stimulation, would accord well with Nahum and Hoff's analogous findings on extrasystoles elicited in the "proximal" zone, but would accord equally well with the dipole theory. The presence of a high R wave in the right ventricular electroendocardiogram in cases of left ventricular extrasystoles (Hecht; Battro and Bidoggia) could be interpreted as being due to the origin of the extrasystoles in the "distal" area. The close resemblance of supraventricular beats in the right ventricular electroendocardiogram and in a simultaneously recorded praecordial lead obtained from a point immediately above the endocardial-electrode (Kossmann *et al*, 1948, Fig. 11) tends to support Nahum and Hoff's views However, since the exact position within the right ventricle of the endocardial electrode cannot be ascertained and the praecordial lead can be considered to be only an approximation to a direct epicardial lead, further investigations have to be awaited until more definite conclusions can be drawn

Vectorcardiography

The possible value of vector diagrams for the determination of the site of origin of extrasystoles was already pointed out by Mann whose "Monocardiogram" is one type of frontal vectorcardiogram (Mann 1931, 1938), also by Schellong (1939). Another early attempt along similar lines (Hollmann and Guckes, 1939), based on a "Triogramm" (a vector recorded by three leads by means of a specially adapted Braun's tube), proved unsatisfactory regarding delimitation of such focus of origin in any definite portion of the heart With the more recent dev [illegible] con- sidered by several authors [illegible] ventricular extrasystoles [illegible] The most comprehensive application so far of vector methods to this problem is that of Donzelot, Milanovich and Kaufmann. It is claimed that the kind of vectorcardiography and electrovectorcardiography as developed by this group of workers makes the location of ventricular extrasystoles a matter "d'une étrange simplicité". "Vectograms" are recorded by a cathode-ray tube in one of three planes from two unipolar leads as follows: frontal (V-6, V-F), horizontal (V-2, V-6), and sagittal (V-2, V-F) In the frontal "vectogram" origin of the extrasystole in the right or left, and upper or lower part of the heart can be determined by the inclination of the QRS loop; the horizontal "vectogram" provides additional information as to anterior or posterior location of the focus If "vectograms" in these two planes are available a ventricular extrasystole can be classified in a more detailed way, for example as left posterior and superior, or as right, anterior and inferior, and from such information the part of the ventricle can be deduced where the ectopic beat arose. In support of this view these authors point out (a) that if the [illegible]

in the exposed hearts of animals and man While we cannot claim any personal experience in vectorcardiography we should like to state by way of general comment that both these

arguments seem to us unconvincing: the first, because the criteria for determining the site of origin of ventricular extrasystoles in any scalar lead are still controversial, the features of such records depending also on factors other than the site of origin of the ectopic beat; the second, because results obtained in artificially elicited ectopic beats in such conditions are applicable to the localization of the site of origin of spontaneous extrasystoles in man only with the greatest reserve because of the modifying influence of many factors (for example, position of the heart, exposure of the organ, electrical properties of surrounding media, manner of spread) Even if the direction of the loops in "vectograms" in various planes made possible an exact spatial localization of the focus, its location in a definite portion of the heart would still not have been established, this would only be possible if the anatomical position of the heart in relation to the three axes could accurately be determined from the "vectograms"

It seems to us that recent developments in vectorcardiography are promising in furthering the elucidation of this problem, but that the present stage is only a beginning as Donzelot *et al* themselves say. "L'étude des extrasystoles ventriculaires est d'ailleurs loin d'être close"

Clinical Applications

Compared with the great physiological interest of these more recent investigations their clinical importance is, as yet, small One clinical application seems to be the determination of the site of myocardial infarction in cases of coronary occlusion, for which some experimental basis is already laid. The occurrence of ventricular extrasystoles in cases of myocardial infarction is, of course, frequently observed, and there are good reasons to assume that they originate in the partially ischaemic border zone between the infarcted area and normal muscle (Harris and Rojas, 1943) In view of this, Hoff and Nahum (1945) correlated in experiments on thirteen dogs the shape in the electrocardiogram of spontaneous ventricular extrasystoles and the direction of the displacement of the S-T intervals in leads 1 and 3 resulting from local myocardial ischaemia which was produced in four different areas of the heart by ligating branches of the coronary arteries, namely, in the right lateral, left lateral, anterior and posterior portions of the myocardium In all cases complete agreement was found between

1 the position and course of the occluded artery,
2 the region of the heart which became cyanotic,
3 the pattern of the S-T displacement, and
4 the configuration of the extrasystoles in the two leads

The appearance of extrasystoles in the standard leads may thus be helpful to determine the site of myocardial infarction This method might lend itself to be further developed by being extended to chest and unipolar limb leads and eventually to be applied to the localization of myocardial infarcts in clinical cases, but we are aware of considerable difficulties which are likely to arise

AURICULAR EXTRASYSTOLES

Compared with the amount of work and thought lavished on the localization of the site of origin of *ventricular* extrasystoles, that of *auricular* ones has attracted far less attention This is understandable for various reasons the greater frequency of ventricular ectopic beats, the larger size and the more conspicuous variations in shape of their deflections in the electrocardiogram, the greater mass of ventricular musculature, the presence of a well-defined conducting system in the ventricles, the recognized great clinical importance of multiform ventricular extrasystoles and the ominous significance of ventricular fibrillation of which these may be the precursors. all these factors make the study of the site of impulse

formation of ventricular extrasystoles appear more important and promising than that of their auricular counterparts. All the same, a more intimate knowledge of the site of impulse formation (and mode of spread) of auricular extrasystoles may in future well become of greater physiological and clinical importance than may be obvious at present. For, quite apart from any intrinsic interest of this problem, auricular extrasystoles are so often the precursors of other disorders of auricular rhythm, such as auricular fibrillation, flutter and paroxysmal tachycardia, that any such increase in knowledge appertaining to auricular ectopic beats may in its train bring about a better understanding of auricular arrhythmias generally

It is to be expected that, the nearer to the normal pacemaker an auricular extrasystole originates, the more closely does its P wave resemble that of the sino-auricular beats. This was established by Lewis in 1910, in the early days of electrocardiography. In experiments on dogs he found that, in lead 2, auricular premature beats elicited by induction shocks showed normal P waves only if they were produced from points in close proximity to the sino-auricular node, that is, from the superior vena cava—auricular junction. An instructive tracing is to be found in Lewis's monograph (1925c) Those from the inlet of the inferior vena cava showed small polyphasic P waves with a tendency to isoelectricity (*see also* Lewis and White, 1914, Figs. 2 and 5), those from the inlet of the pulmonary veins usually yielded P waves which started with an inverted phase Those from the interior of the right auricle, namely the coronary sinus, showed also inverted P waves, and in one such instance the P-R interval was shortened and the origin of the premature beat was considered to be very near the A-V node Upright P waves, but differing in outline from normal ones, were found in extrasystoles originating in the base and tip of the right auricular appendix In the same paper Lewis applied these experimental findings to the interpretation of human curves Using lead 2, he distinguished three main types of auricular extrasystoles in man:

(1) those with upright P waves in which cases the ectopic beat was considered to originate in the upper regions of the auricle, in the neighbourhood of the S-A node;
(2) with inverted P waves these were taken to indicate origin in the " lowest regions of auricular musculature ", namely, in the neighbourhood of the A-V node or, in the absence of a shortened P-R interval, possibly in the region of the pulmonary veins,
(3) those with isoelectric or diphasic P waves, signifying impulse formation in the middle part of the auricle, the neighbourhood of the inferior vena cava, or pulmonary veins, or appendix of the left auricle

Lewis concluded " An absolute localization is of necessity impossible at the present stage of the enquiry, nevertheless localization is obviously possible within certain limits " (p. 34) And this conclusion still holds good after about forty years. While in many other fields of electrocardiography great progress has been made during that period, our knowledge in this particular question has not materially advanced The realization of the importance of intra-auricular disturbances of conduction in relation to the shape of P waves (Scherf and Shookhoff, 1926; Rothberger and Scherf, 1927) has brought into relief an important difficulty in the elucidation of this problem If abnormal conduction in the auricles can alter the shape of P waves to such an extent that inverted P waves can, in certain circumstances, be observed in cases of unquestionable sinus rhythm, and A-V beats can be associated with upright P waves, it is no longer possible, unreservedly, to consider the shape of P waves as indicative of the site of impulse formation within the auricles This consideration alone also invalidates Schellong's attempt, dubious in many other respects, at localization of auricular beats from the shape of P waves in three special leads, each recorded from two points on the anterior chest wall, the lines of the leads all passing through the centre of the auricles projected on to the anterior chest wall (Schellong, 1926).

It is certain, however, that auricular extrasystoles originating in the lower parts of the auricles, near the A-V node, show a very low positive P wave in lead 1 and deep sharply inverted P waves in leads 2 and 3. This pattern of P waves in the standard leads is typically seen in A-V rhythm.

In the augmented unipolar extremity (aV) leads extrasystoles originating in the upper parts of the auricles, near the sinus node, show inverted P waves in lead aVR and upright P waves in lead aVF. With a focus of origin of the extrasystoles in the area near the auricular part of the A-V node, the P waves are upright in aVR and inverted in aVF (*see* Fig 58).

Oesophageal leads, in which the exploring electrode is in close proximity to the left auricle, lend themselves to the study of this problem. Brown (1936) drew attention to the importance of the moment of onset of the intrinsic deflection of the extrasystole, which indicates the moment of activation of the area beneath the exploring electrode. If, in the oesophageal lead, the extrasystole starts immediately with the intrinsic deflection, the conclusion seemed warranted that the extrasystole originated almost exactly beneath the oesophageal electrode. In one such instance (*see* his Fig 12, p 26), the total duration of the P wave of the premature beat was lengthened to 0 1367 second from the 0 0849 second of the normal P waves Brown interpreted this as indicating a different path of spread through the auricles of the ectopic beat A similar observation is contained in a paper by Wunsche (1945) Using an oesophageal lead in which the exploring electrode was paired with a central terminal (Wilson), he obtained upright P waves of normal beats whereas those assumed to have originated in the left auricle yielded inverted ones; their downstroke started immediately This " intrinsic " deflection was often split; this was attributed to a different intra-auricular spread of the ectopic impulse, and the slight lengthening of the intra-auricular conduction time supported this explanation In view of the grave doubts which have recently been cast on the possibility of identifying an intrinsic deflection the interpretation of these investigations has to be accepted with great reserve; *see also* p. 377 (" Spread of the Excitation "), *also* Brown (record 4 of his Fig 24, p 41) Both Brown's and Wunsche's observations illus-

If praecordial leads are employed for such investigations the choice of the indifferent electrode is of great importance A central terminal is far preferable to either CR or CF leads since, in the latter, the potential differences of the indifferent electrode exert a profound influence on the shape of the P waves (Brown and Ellis, 1947)

The more recently developed technique of the recording of intracavity potentials by means of cardiac catheterization has yielded some further information about this problem, without as yet contributing much to the determination of the site of origin of spontaneous auricular extrasystoles. For, just as with ventricular extrasystoles, there is every reason to assume that auricular ones occurring during catheterization are elicited by the exploring electrode, by means of mechanical stimulation of the endocardial surface of the (right) auric

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favourable for eliciting extrasystoles by being in intermittent contact with the wall of the chamber (*see also* section on " Catheterization ") Auricular premature beats were found by Levine *et al* in four out of twenty-one studied subjects Usually the P waves of the extrasystoles started with a sharp downward deflection, interpreted, according to the dipole theory,

as being the "intrinsic" deflection and indicating that, at that time, the impulse travelled away from the electrode. The inference is that the contact of the tip of the electrode actually elicited the ectopic beat In one instance it was found that, while in the intracavity lead the P waves of the ectopic beats differed somewhat from that of normal beats, such differences were more pronounced in lead V-2, simultaneously recorded; the assumption seemed justified that, in this case, the praecordial electrode was nearer to the site of ectopic impulse formation than the intracavity one In only one case were four auricular extrasystoles observed in succession, all showing sharply inverted P waves, which, however, differed in shape somewhat from one another Simultaneously recorded intracavity and oesophageal electrocardiograms, both electrodes being inserted at the same vertical distance from the suprasternal notch, showed that the "intrinsic deflection" of normal beats occurred in the oesophageal electrocardiogram 0 05-0·07 second later than in the right auricular electro-endocardiogram In the case of auricular extrasystoles this delay was increased to 0·11 to 0·13 second This is interpreted as indicating "that the impulse arising at the ectopic site at or near the tip of the intra-auricular electrode pursued a longer course to the point in the left atrium tapped by the oesophageal electrode than impulses arising in the normal pacemaker" (Levine *et al*, 1949)

ECTOPIC IMPULSE FORMATION AND SPECIALIZED TISSUE

Another aspect of the problem of localization of the focus of origin of extrasystoles, and of ectopic impulses generally, is the question whether the origin of such beats is confined to specialized tissue or whether they can also originate in the common myocardium.

Although, for reasons discussed below in this section, the problem has now lost much of its importance, it seems desirable to discuss it briefly as it had given rise to considerable *controversy in the past and in its investigation some findings of more general physiological* interest were obtained

The view that ectopic beats can originate only in the specialized tissue was attractive from the start because of the fact that the *normal* impulse originates in such specialized tissue. Some early observations seemed to support this view Of these, Marchand's findings may be mentioned that one make shock applied to the A-V border of a frog's heart produced several contractions, Gaskell's analogous findings regarding a mechanical stimulus applied to this region, and Tigerstedt and Strömberg's similar observations made on the sinus of the frog's heart, though such repetitive response to one stimulus could be obtained from various portions of the heart (*see* chapter on "Mechanism") However, the assumption that the specialized tissue is the only one which may give rise to ectopic beats was supported by Mackenzie, by Lewis and Silberberg, and by Koch Ishihara and Nomura found automatic impulse formation in the "spurious tendons" of the dog's heart, while it was absent in the common muscle fibres. Lewis, in the last edition of his classical monograph, stated (1925): "There is little to suggest that extrasystoles can spring from ventricular muscle as opposed to Purkinje tissue . "

Even if automatic impulse formation was found in strips of the common myocardium the presence, in such strips, of specialized fibres could not be excluded. Actually, it was found histologically in many of them and spontaneous rhythms were more pronounced in those which contained such fibres (Greene and Siddle). The smallest groups of specialized fibres were found to be capable of initiating spontaneous contractions (Skramlik)

The difference in the effect, upon ectopic impulse formation, of warming different portions of the heart in dogs sensitized by the systemic application of small doses of barium seemed to support this view If such small doses of barium were used that no alteration in cardiac rhythm resulted, warming, by means of a thermode, of any part of the *ventricles* elicited ectopic tachycardias originating in the warmed area Warming of the *auricles*, on

the other hand, at a distance of the S-A and A-V nodes failed to precipitate such ectopic arrhythmias The inference was that the ectopic ventricular tachycardias were due to the enhancing effect of warming upon the specialized system (Purkinje ramifications), so that the automaticity of the warmed portions of this system exceeded that of the S-A node and thus became the pacemaker In the auricles, on the other hand, this effect was absent because specialized fibres were absent (Scherf, 1927 a and b)

The frequent occurrence of ectopic arrhythmias during catheterization was interpreted as supporting the origin of such ectopic impulses in specialized tissue, namely, the subendocardial network of Purkinje fibres (Landtman)

Support for the opposite view was not lacking, namely, that ectopic impulse formation may take place in the common myocardium, being independent of specialized tissue Taussig and Meserve found rhythmic stimulus formation in isolated strips of the myocardium and even questioned whether isolated specialized tissue, without any common myocardial fibres attached, was capable of automatic impulse formation. In the hearts of rabbits and guinea-pigs Rothberger and Sachs investigated spontaneous impulse formation in isolated strips of the outer wall of the left auricle, or of the apex, and found it present in seven out of sixty-five preparations If aconitine or veratrine was added to the nutrient (Soejima's) solution rhythmic activity was observed in all preparations In these portions of the heart specialized tissue is thought to be absent and, in fact, Aschoff's histological examination of such strips failed to demonstrate it Rothberger and Sachs concluded that ectopic impulses may be formed independently of specialized tissue Moreover, *topical* application of various compounds (sodium chloride, barium chloride, strophanthin, digitalis, aconitine, veratrine) to any part of the dog's heart *in situ*, ventricle or auricle, even appendix of the left auricle, results in ectopic impulse formation and ectopic tachycardias originating at the site of application These studies are discussed in the appropriate sections of this book ("Extrasystoles and Drugs and Electrolytes")

The conclusions drawn from such observations had to be modified in view of the more recent discovery that the ramifications of the specialized system were far more extensive than previously assumed It was found that such fibres, contiguous with and structurally alike the subendocardial network, extended throughout the myocardium to within a few mm of the epicardial surface The relevant investigations are discussed in the section on "Spread of the Excitation " (p 374), where it is also pointed out that the histological differentiation between specialized and common myocardial fibres is fraught with difficulties On the other hand, none of the various claims to have demonstrated specialized fibres in the auricles have stood the test of more careful histological re-examination and none of such fibres could be shown to possess the capacity of automatic impulse formation

The *conclusions* to be drawn from such contradictory findings seem to be that in certain experimental conditions ectopic impulse formation is possible in any part of the heart Whether the presence of specialized tissue is indispensable remains undecided. The observation that skeletal muscle may, in certain circumstances, show rhythmic impulse formation would seem to s[illegible] tion is therefore admittedly only conjectural

SUMMARY

Ventricular Extrasystoles

The determination of the focus of origin of ventricular extrasystoles, while until recently considered to have only an academic, if any, importance, has become of increasing

consequence during the last twenty years, since such investigations proved to be of considerable moment in connexion with other problems of cardiac physiology and pathology and, of late, with the interpretation of the electrocardiogram generally.

The various stages in the research on this problem can conveniently be divided into four periods:

First Period

From the investigations of Kraus and Nicolai starting in 1907 up to those of Rothberger and Winterberg in 1913 and of Lewis in 1916. Much of the work published at this stage is now only of historical interest. This applies, for instance, to the controversy whether the direction of the initial deflections signified a right-left ventricular or apical-basal origin of the ectopic beat, neither of which views has in this form stood the test of time. The importance of the lead employed was often not realized, although as early as 1908 Einthoven stated that lead 1 distinguished between right and left half of the heart and lead 3 between apical and basal portions; upward directed deflections in lead 1 he considered indicative of origin of the ectopic impulse in the right, downward ones in the left half of the heart, upward and downward directed deflections in lead 3 he assumed to signify basal and apical origin respectively As far as a right-left ventricular or apical-basal localization can be at all deduced from the direction of the initial deflections in the various limb leads this early view of Einthoven's has been shown to be remarkably correct by subsequent investigations, some of them comparatively recent.

Second Period

From the investigations of Rothberger and Winterberg in 1913 and those of Lewis in 1916 to those of Barker, Macleod and Alexander in 1930. Rothberger and Winterberg concluded from extensive experimental observations that the factor which determined the shape in the electrocardiogram of ventricular ectopic beats was the location of the stimulated point in relation to the point of the specialized conducting system whence the further spread of the excitation took place. The work of this period which was to have the most lasting effect was that of Lewis in whose opinion extrasystoles showing downward initial deflections in lead 1 and upright ones in lead 3 arose in the right ventricle, whereas left ventricular ones yielded upright initial deflections in lead 1 and downward ones in lead 3. This interpretation prevailed until 1930

Third Period

From 1930, when the observations of Barker, Macleod and Alexander on an exposed heart in man threw doubt on Lewis's interpretation, to about 1940 when the extensive experimental investigations of Nahum, Hoff and collaborators started. As a result of direct stimulation of a human heart exposed at operation Barker, Macleod and Alexander arrived at the conclusion that Lewis's terminology should be reversed, namely, that the direction in the various limb leads, which Lewis took to indicate right ventricular, actually signified left ventricular origin and vice versa. This entailed, not only a reversal of the terminology regarding the side of origin of ventricular ectopic beats, but also a similar reversal in the interpretation of bundle branch block curves and the necessity of new explanations of right and left ventricular preponderance. During the subsequent decade the observations of Barker, Macleod and Alexander were confirmed, and the reversal of the terminology regarding the interpretation of electrocardiograms in relation to the side of origin of extrasystoles, and of those of bundle branch block curves, was supported by experimental and clinical observations. At the same time it was realized that the new terminology was only applicable with certain qualifications. The importance of the position of the heart and of the structure of the surrounding tissues was realized as accounting for some of the exceptions

encountered in some instances, clinical as well as experimental Other exceptions had not found a satisfactory explanation, such as the occasional occurrence of "left" or "right" ventricular extrasystoles elicited from portions of the contralateral ventricle. The meaning of concordant and discordant tracings was obscure and the applicability of findings obtained in cases of bundle branch block to those of extrasystoles and vice versa was not entirely clarified

Fourth Period

From 1940 to the present. This phase is dominated by the extensive investigations of Nahum, Hoff and collaborators. Starting from a reinvestigation of the dual nature of the normal electrocardiogram as a resultant of dextro- and laevocardiogram, these workers, by eliminating the surface potentials of known portions of the heart, claimed to have established four basic patterns of extrasystoles

(1) right lateral, concordant, main initial deflection upward in all limb leads, origin of extrasystole in the "centre" of the right ventricle, that is, equidistant from the septum;
(2) left lateral, concordant, main initial deflection downward in all limb leads; origin of extrasystole in the "centre" of the left ventricle,
(3) anterior septal, discordant, main initial deflection downward in lead 1, upward in lead 3, origin of extrasystole at or near the anterior septum,
(4) posterior septal, discordant, main initial deflection upward in lead 1, downward in lead 3, origin of extrasystole at or near the posterior septum.

Certain exceptions were shown to be due to the activation of portions of the contralateral ventricle in advance of the one in which the extrasystole had been elicited. The limits within which the findings obtained in cases of bundle branch block were applicable to those of extrasystoles and vice versa became better understood The observation that extrasystoles elicited from a point of the epicardium and from one immediately subjacent of the endocardium were indistinguishable in the electrocardiogram was made again (but objections to the technique were raised) and its great importance for the interpretation of the electrocardiogram generally was realized For this observation, if confirmed, is not compatible with the current dipole theory of the electrocardiogram, according to which the direction of the spread of the excitation wave in relation to the exploring electrode determines the direction of the deflection in the record. As a result of further investigations, which included the use of chest leads, this school of workers developed a new conception of the genesis of deflections in the electrocardiogram, termed "zonal interference" theory. According to this, the electrocardiogram of unipolar leads is the result of only two opposing forces the excitation of a proximal region, that is, at or near or facing the exploring electrode, producing a downward deflection (negativity of the exploring electrode), and that of a distal region, facing away from the exploring electrode, resulting in an upward deflection, the two zones being separated by an intermediate zone; the deflections in the record were found to be independent of the pathway by which the excitation arrives The proximal, distal and intermediate zones were determined for the three unipolar limb and for two unipolar chest leads. Since, in the three unipolar limb leads, these three zones overlap it was attempted, by simultaneously recording two or three unipolar limb leads, to delimit the site of origin of extrasystoles within a far narrower area than had been possible by using only one unipolar limb lead. By simultaneously recording one bipolar and two unipolar limb leads it was attempted to determine the mechanism underlying the appearance of upright or inverted deflections of extrasystoles

leads alone At the present moment it does not seem possible to reconcile the observations of this school of workers with the current theory of the origin of deflections in the electrocardiogram, on its part based on a wealth of experimental and clinical observations. These investigations are, at present, not confirmed. Moreover, vectoranalysis and vectorcardiography have demonstrated that *all* parts of the heart contribute to the electrocardiogram at any moment in any lead, that regarding the contour of the electrocardiographic record the degree of proximity of the exploring electrode is of far less importance than believed in the past, and that our conceptions about the determination of an intrinsic deflection as indicating the arrival of an excitation beneath the exploring electrode need reconsideration For these reasons grave doubts exist about the validity of the zonal interference theory. Any judgment of the significance of these investigations must of necessity be provisional.

The results of more recent investigations by means of *oesophageal leads*, by *records of intracavity potentials* obtained with cardiac catheterization, and by *vectorcardiograms* are briefly reviewed

The use of the shape of extrasystoles as an additional criterion for the localization of the site of myocardial infarction is briefly discussed.

Auricular Extrasystoles

The nearer to the normal pacemaker an auricular extrasystole originates, the more closely does its P wave resemble that of the sino-auricular beats Lewis, who established this fact in 1910, distinguished three main types, according to the shape of the P waves in lead 2, namely, origin of the ectopic beat in the upper auricular portions, characterized by upright P waves, in the lowest regions of auricular musculature, showing inverted P waves, and those giving rise to isoelectric or diphasic P waves, the origin of which he believed to be in the middle portions of the auricle It was subsequently realized that the shape of the P wave of an auricular extrasystole cannot unreservedly be taken to indicate its site of origin, since intra-auricular disturbances of conduction may profoundly modify the appearance of these waves More recently attempts have been made to determine the site of origin by the time at which the "intrinsic deflection" occurs in the oesophageal electrocardiogram: immediate occurrence was taken to indicate that the ectopic beat arose in close proximity to the exploring electrode. The results so far obtained with recording of intracavity potentials by means of cardiac catheterization, which are briefly discussed, have not yet brought any significant advance in our knowledge of this problem To a certain extent this is due to the difficulty in determining the beginning of the "intrinsic" deflections It is pointed out that, in view of the close relationship between auricular extrasystoles and other disorders of auricular rhythm, the study of the site of origin of auricular ectopic beats may well be of a greater importance than is attached to it at present, since it is likely to result in a better understanding of auricular arrhythmias generally.

Origin of Extrasystoles and Specialized System

Regarding the question whether extrasystoles originate only in the specialized system or whether they can arise in the common myocardium, the relevant literature is reviewed It is concluded that in certain experimental conditions ectopic impulse formation is possible in any part of the heart In view of more recent findings that the ramifications of the specialized system are far more extensive than previously assumed it remains undecided whether the presence of specialized fibres is indispensable for the origin of ectopic beats.

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CHAPTER XI

SOME MAINLY CLINICAL ASPECTS OF EXTRASYSTOLES AND OF ECTOPIC BEATS GENERALLY

EXERCISE

The usual effect, upon extrasystoles, of physical exercise is their disappearance during and immediately after exertion In a minority of cases exercise precipitates, or increases the number of previously present, extrasystoles Increase in rate of ectopic tachycardia, resulting from physical exertion, is observed in rare instances Each of these possibilities merits a brief discussion

Disappearance of Extrasystoles on Exertion

Magnan's observation (1877) that exercise abolished " certaines intermittences du pouls" may well have referred to extrasystoles. In clinical practice it is indeed a common experience that a patient seeks medical advice because he is worried about his heart missing beats, which he noticed after going to bed, or on other occasions when he was at rest, whereas he forgets all about it while going about his daily routine what sensations the premature beats may have caused in the individual case, disappear with the extrasystoles during activity Such observations, indicating that the arrhythmia occurred only during rest and was abolished by even mild exertion, are of diagnostic as well as therapeutic interest diagnostic because, if extrasystoles are absent during examination, such a history points strongly to their being the cause of the symptoms (*see* section on " Differential Diagnosis "); therapeutic, because lay people often realize nowadays that structural heart disease tends to manifest itself during exertion rather than during rest and thus the patient's own observation about the timing of his trouble, suitably explained, can with advantage be used to convince him of the harmlessness of his complaint

The disappearance of extrasystoles as a result of exercise is partly due to the ensuing increase in heart rate, with shortening of the diastolic intervals, and partly to nervous influences upon the heart (*see* chapter on " Nervous System ")

An unusual observation in which exercise converted ventricular tachycardia with alternation of the complexes in the electrocardiogram into sinus rhythm—a particularly striking example of suppression of an ectopic arrhythmia by exercise—is a case described in a somewhat different context by Scherf and Kisch (Case 2) The patient, a man of twenty-one (who

plexes (Fig 187a) They were separated by one or two sinus beats (Extrasystolie à paroxysmes tachycardiques) Moderate exercise (40 genuflexions) converted the tachycardia into bigeminal rhythm with constant shape of the extrasystoles (Fig 187b) Fig 187c, taken five minutes after the end of exercise, shows that the ventricular tachycardia re-established itself In this patient more severe exertion resulted in the temporary establishment of sinus rhythm, as illustrated by Fig 188, obtained on another day. Fig. 188a demonstrates bigeminal heart action after moderate exertion (30 genuflexions) When, at this

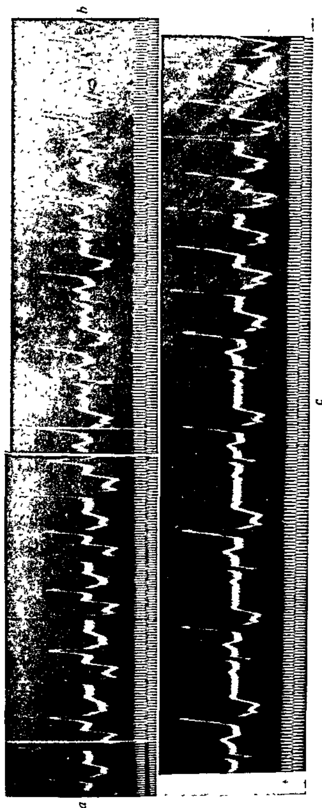


FIG 187.—*a*: Before exercise Ventricular tachycardia with alternation of shape of the ventricular complexes *b*: after moderate exercise. Bigeminal rhythm *c*: five minutes after the end of exercise Re-appearance of ventricular tachycardia.

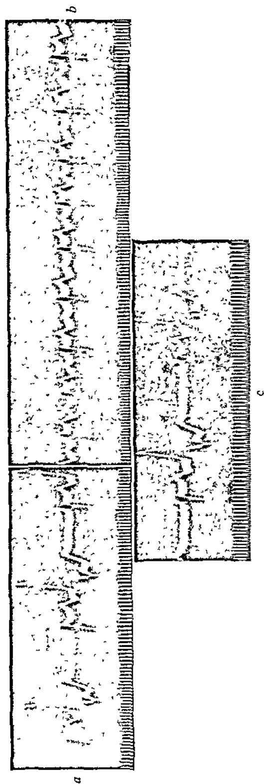


FIG 188 —*a* After moderate exercise Bigeminal rhythm *b* After the same amount of exercise carried out again after the recording of *a* Sinus rhythm *c* Five minutes after *b* Recurrence of bigeminal rhythm

stage, the same amount of exercise was carried out again, sinus rhythm ensued (Fig 188b), but five minutes later bigeminal heart action was again present (Fig. 188c).

In this case, in which also digitalis and quinidine abolished the arrhythmia temporarily, it was not possible to restore sinus rhythm for any length of time and the patient died after five years from congestive heart failure. Necropsy showed a grossly enlarged heart without hypertrophy or any structural (macroscopic or microscopic) abnormality—a remarkable illustration of fatal myocardial weakness resulting entirely from disturbances in the cardiac dynamics

Precipitation of Ectopic Arrhythmias by Exercise

The reverse effect, upon extrasystoles, of exercise, namely, precipitation of the arrhythmia or increase in the number of previously present premature beats, while not so common, is by no means rare Patients responding to exertion in this way usually, but not invariably, suffer from structural or toxic heart disease. A few relevant papers may be briefly discussed

In an investigation on thirty-five normal children with extrasystoles, Lyon and Rauh found *after exercise an increase in the number of the premature beats in four and a decrease in fourteen cases*

Bourne examined this question in normal subjects and in patients with various forms of heart disease During the period after exercise, in which the heart rate dropped to its resting level, seven out of eight normal subjects showed a decrease in the number of extrasystoles, or no change was observed In patients with rheumatic heart disease similar conditions were found In nine out of eleven patients with arteriosclerosis, on the other hand, the number of premature beats increased after exercise. We concur with Bourne's interpretation that this was due to ischaemia in some parts of the heart, resulting from coronary sclerosis Such increase in the number of premature beats after exertion was seen by several investigators (" arhythmie d'effort ", " crises extrasystoliques ", Josue and Heitz; Luten; Wilson and Robinson, Otto and Gold, Gallemaerts and van Dooren)

Klemola studied this problem especially in connexion with infectious diseases. Amongst 215 patients who had just recovered from some infectious illness, extrasystoles after exercise were found in twenty-seven; eighteen of these had had diphtheria, the remaining nine some other infection (for instance, tonsillitis, scarlet fever, pneumonia). In twenty-three of these cases extrasystoles occurred only after exertion (Klemola, 1942) In a later study, devoted to the effects of diphtheria in children, he found extrasystoles after exercise in eighteen out of forty-one cases, in seventeen of these the premature beats occurring only after exertion (Klemola, 1944)

Kienle considers as pathological all extrasystoles which occur immediately or within a few minutes after exercise According to him an abnormal condition of the heart must be assumed also if exercise fails to abolish existing extrasystoles.

A personal observation may be added in which exercise precipitated, not only extrasystoles, but also paroxysmal tachycardia (Scherf, 1924) (*see also* Gallavardin) The records (Fig 189) were obtained from a forty-four-year-old woman without evidence of heart disease, who complained of palpitation on exertion. At rest, this patient always showed sinus rhythm (Fig 189a). Twenty-five genuflexions precipitated ventricular paroxysmal tachycardia, the rate of which was 212 per minute, but soon dropped to 183 (*see* Fig. 189b and c) As the rate slowed down further, an increasing number of sinus beats were observed, separated by a steadily diminishing number of extrasystoles, (*see* Fig 189, d and e), until finally sinus rhythm was re-established. In this patient exercise had invariably the described effect upon the cardiac rhythm.

Denolin reported a case of complete A-V block in which exercise precipitated attacks

of paroxysmal ventricular tachycardia with varying shape of the ectopic ventricular beats

There is ample evidence of auricular fibrillation occurring after exercise in healthy subjects (Jervell, Kienle)

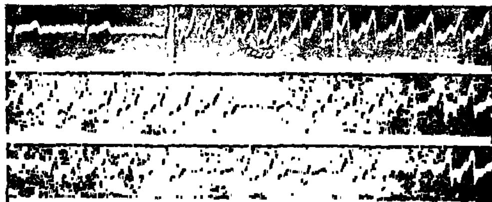


FIG. 189—*a* At rest Sinus rhythm *b-e* various degrees of ectopic ventricular tachycardia and arrhythmia after exercise Time base 0 04 second From SCHERF, *Wien Arch inn. Med*

Increase by Exercise of the Rate of Ectopic Tachycardia

This effect of exercise upon ectopic—auricular or ventricular—tachycardia is rare. Instances have been described by Wenckebach and Winterberg, Wilson *et al* (1932), Scherf and Weissberg Fig. 190, taken from Scherf and Weissberg's paper (Case 4), provides an example. It was obtained in a man of forty-eight, a heavy smoker who complained of precordial pain and palpitation on exertion At rest, ventricular extrasystoles occurring in

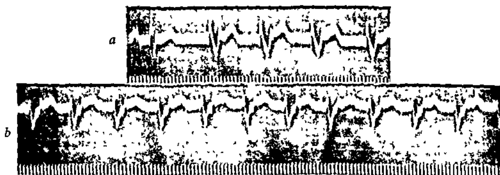


FIG 190—Lead 2 Increase in rate of ventricular ectopic rhythm from 100 (a) to 130 (b) resulting from moderate exercise Time base: 0 04 *second*

groups of four or five were present, some slowing of the ectopic rhythm being observed in respect of the last two extrasystoles of each group After exercise (knee-bending fifteen times) the number of extrasystoles increased considerably as well as their rate, *for example* from 100 to 130 (*see* Fig 190b as compared with Fig 190a) It is reasonable to assume that

this was due to a sympathetic nervous effect: this view is supported by the experimenta observation that stimulation of the sympathetic increases the rate of ectopic ventricula tachycardia produced, in dogs, by the focal application of hypertonic solutions of bariun or sodium chloride to the epicardial surface of the exposed heart *in situ* (Piccione anc Scherf).

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POSTURE

The frequent occurrence of extrasystoles in the supine position is a well-known fact. A great many patients find that they are only or mainly aware of the "missed beats" when they are in bed and settling down for a night's rest. Several factors are likely to be responsible during the daily activities the patient's attention is diverted whereas at night such arrhythmias are more likely to obtrude themselves; the slower heart rate and nervous factors also play their part Many patients, however, insist that rest in a chair will not precipitate the arrhythmia whereas the horizontal position will invariably do so. Moreover, in some individuals extrasystoles occur only while lying on one particular side. There is thus a definite positional element in a proportion of cases.

Lyon and Rauh found in twenty-two children that change from the supine to the erect posture increased the number of extrasystoles in four, and decreased it in seven instances.

An observation of ventricular extrasystoles (namely short runs of ventricular tachycardia) occurring in an otherwise healthy woman of twenty-four only on assuming the erect posture was reported by Peters and Penner; it was attributed to an unusually strong sympathetic tone on this change of position An increase in the number of extrasystoles and the occurrence of auricular paroxysmal tachycardia on assuming the erect posture were observed by Fine and Miller in a girl of sixteen.

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EXTRASYSTOLES IN RELATION TO VARIOUS TYPES OF CARDIOVASCULAR DISEASE

Coronary Disease

Experimental Investigations

Arrhythmias following ligation of coronary artery branches were observed long before any detailed analysis of such irregularities by modern methods was possible (Bezold 1867, Porter 1894, 1896), and the importance of such disturbances of rhythm in causing sudden death of patients with coronary disease was recognized by Cohnheim and Schulthess-Rechberg as early as 1881

In the first systematic investigation on cardiac arrhythmias elicited in dogs by ligation of the descending branches of the right or left coronary artery extrasystoles were recorded (Lewis, 1909) Usually, such ectopic beats were ventricular in origin, but after ligation of the right coronary artery nodal and auricular extrasystoles were also observed (Lewis, Smith, Kisch) The shape of the extrasystoles varied continually and sometimes ventricular extrasystoles with retrograde conduction to the auricles as well as interpolated varieties were seen In some experiments, however, extrasystoles were completely absent.

The time of occurrence of such ectopic beats varies, often they are observed within one minute after ligation, but sometimes a much longer interval elapses, for example, forty-six minutes (Goldenberg and Rothberger), or even one week, as observed in one monkey by de Waart, Storm and Koumans (1936b)

The incidence of ectopic beats after ligation of coronary branches varies according to different investigators, but seems to be about 35–50 per cent on an average Thus Harris and Hussey saw them in fifteen out of fifty dogs within fifteen minutes after ligation, followed by ventricular fibrillation. In monkeys, de Waart and collaborators saw them in six out of seventeen experiments following ligation of the descending branch of the left, and in six out of fifteen instances after that of the right coronary artery In another series (Blumgart, Gilligan and Schlesinger), in which nembutal and ether were used as anaesthetics, they occurred in 50 per cent of thirty-nine dogs and were observed particularly frequently in those which later developed ventricular fibrillation The one dissenting report of Damir and Lampert that up to three hours after ligation of coronary arteries no extrasystoles were observed in dogs anaesthetized with morphine and ether can be disregarded This report is strange, because in six out of ten dogs coronary artery ligation (*ramus descendens ant*) caused ventricular fibrillation, and paroxysmal tachycardias were also observed

No constant relationship seems to exist between the site of origin of ventricular extrasystoles and that of the ligated coronary artery branch In one series of experiments only were right-ventricular extrasystoles found after ligation of the right, and left-ventricular ones after that of the left coronary artery (Clerc, Deschamps, Bascourret and Levy), but all other investigators reported right- or left-ventricular ectopic beats with ligation of either coronary artery This is rather surprising in view of the available evidence, discussed on p 401 and below in this section (p 420), that the ectopic beats originate in the boundary zone between the ischaemic and non-ischaemic areas

In a typical experiment extrasystoles occur at first singly Then the intervals between the ectopic beats become successively shorter while their number increases The next stage is polygeminy, and short attacks of ectopic tachycardia follow, culminating in flutter and

fibrillation. In some experiments ventricular fibrillation sets in without extrasystoles having previously occurred; this was observed in six monkeys by de Waart and his collaborators. In other experiments extrasystoles gradually disappear without any more pronounced arrhythmia occurring. Longer chains of bigeminal rhythm are decidedly rare

As had to be expected, injection of obliterating substances into the coronary artery has the same effect as ligation (Hamburger, Priest and Bettman) When in cats air was injected into the jugular vein extrasystoles originating in the right ventricle were recorded; with injection of air into the left ventricle the extrasystoles originated in that ventricle (Pines). Fat embolism has been seen to produce extrasystolesin man (unpublished personal observation)

In spite of extensive experimental investigations the underlying mechanism is only partially understood Spasm, originating by way of reflex from the infarcted area through the vagus as efferent nerve, has been claimed as being partly responsible for such arrhythmias (Manning *et al*, LeRoy and Snyder). It was found that, as compared with conscious dogs, the mortality after coronary ligation in animals anaesthetized with morphine and ether was reduced from 40 to 10 per cent. This difference was thought to have been probably due to vagal paralysis (Manning *et al*) We are not in agreement with this view for several reasons. Amongst them, the failure of an antispasmodic drug, such as aminophylline, to prevent such arrhythmias may be quoted (Mahaim and Rothberger). The absence of struggling of the anaesthetized animals may also well have been of importance in accounting for the above differences.

Quinine also was incapable of preventing such arrhythmias In seven experiments 0·2–0 4 gramme of quinine was injected into dogs immediately after the first ectopic beats had occurred, but in five experiments ventricular tachycardia, and in four ventricular fibrillation were recorded (Goldenberg and Rothberger) Further data on the effect of quinidine in such arrhythmias are given in the section on this drug (p. 292).

General asphyxia of the heart also cannot be considered to play any significant part, for ectopic arrhythmias do not occur in such circumstances (Mathison; Lewis and Master; Motta), though disturbances of conduction and shifting of the pacemaker were seen (Greene and Gilbert) In extrasystoles elicited by aconitine even the reverse effect of asphyxia was observed by Scherf who found it to abolish the extrasystoles in fifteen out of nineteen experiments

In contradistinction to the failure of *general* asphyxia of the heart to have any effect upon ectopic rhythm formation, that of *local* ischaemia has increasingly been realized as of great importance Harris and Rojas put forward good reasons for the assumption that, after ligation of coronary branches, the ectopic beats originate in the ischaemic-nonischaemic boundary zone Local leads obtained from this zone showed abnormally high spikes and also monophasic R-T segments These authors also drew attention to the striking similarity between such rhythms developing as a result of regional ischaemia and those elicited by galvanic current and concluded that certain alterations in the permeability conditions of the cells of that zone may be the common factor. Harris and Matlock found in the mammalian heart that moderate anoxia lowered the threshold to brief electrical stimuli whereas in severe anoxia the threshold rose rapidly. In excised nerve Lehmann found a transient increase in excitability occurring during the first six to eight minutes of asphyxia; during this period spontaneous discharge of impulses may occur. This whole aspect is discussed in more detail in the chapter on " Mechanism ".

Wiggers, Wégria and Piñera showed in experiments on dogs that one to two minutes after occlusion of the *ramus descendens* the fibrillation threshold to rectilinear D.C. shocks of 0 01–0 02 second, applied in the vulnerable period after a contraction, was considerably reduced. At the same time centres of ectopic impulse formation occurred in such circumstances. On the basis of such observations these authors put forward certain views on the

mode of origin of ventricular fibrillation occurring after coronary occlusion In essence, these consist in the assumption that ventricular fibrillation is precipitated by ectopic beats becoming supra-threshold as a result of the lowering of threshold, and that any one of them may thus initiate ventricular fibrillation when it falls in the vulnerable period of either a normal beat or of an ectopic one originating from another ectopic focus This aspect is discussed more fully in the section on "Fibrillation"

Because of the delayed appearance of extrasystoles after myocardial infarction it was claimed that they originate in the area of inflammation surrounding the infarcted area (Froment) Rothberger and Zwillinger found that after ligation of a coronary artery branch smaller doses of strophanthin produced ectopic arrhythmias, since the drug could not have reached the infarcted area these authors tentatively conclud[illegible] that the ectopic beats arose in the zone surrounding the infarct The[illegible] tible with the assumption of Harris and Rojas

More recently [illegible] By effecting the liga[illegible] within an interval of one hou[illegible] [illegible]icular fibrillation and was thus able to investig[illegible] [illegible]opic rhythms In such experiments ectopic beats were observed [illegible] the first ten minutes after the completed occlusion A quiescent period followed of four-and-a-half to eight hours during which little or no ectopic activity was recorded After this latency ectopic beats developed with increasing frequency, the duration of the ectopic activity varying between two and five days While the immediate ectopic rhythm was attributable to the effect of local ischaemia via injury potentials, the long period of delayed ectopic activity was considered mainly due to the effect of products of necrosis

Clinical Observations

These are, on the whole, in accordance with the experimental findings Ventricular extrasystoles and paroxysmal tachycardia following coronary occlusion were reported by Robinson and Herrmann in 1921, and Ebstein and Mackenzie saw extrasystoles frequently during attacks of angina pectoris

A few data about the incidence of such arrhythmias in myocardial infarction may be useful Rosenbaum and Levine saw extrasystoles in 25 per cent of their cases with coronary thrombosis, amongst them ventricular as well as auricular ones As the mortality was 27 per cent in the patients without, and 33 per cent with extrasystoles, these authors denied any prognostic significance of extrasystoles in this condition This conclusion is not in accordance with our experience and that of others and may be due to the fact that these authors used quinidine in adequate doses once such arrhythmias were noticed

Similar findings were obtained by Master, Dack and Jaffe

Padilla and Cossio reported extrasystoles in twenty out of ninety-two cases of myocardial infarction Of these twenty, eight (40 per cent) died, including all four patients with multiform extrasystoles The mortality of the patients without extrasystoles was 38 per cent Woods and Barnes encountered an incidence of extrasystoles of 11 2 per cent. in those of their patients who survived, and of 23 3 per cent in those who succumbed. The number of extrasystoles also seems of importance occasional extrasystoles, not more than one in twenty-one beats, were seen in three patients who survived, and in another three survivors ectopic beats occurred once in eleven to twenty beats More numerous extrasystoles were recorded in seventeen cases, 82 4 per cent of whom died

In Jervell's series of sixty-five patients with myocardial infarction supraventricular extrasystoles were found in nine, ventricular ones in twenty-three, and both types in two instances

Smith, Keyes and Denham studied the records of 920 patients with acute myocardial

infarction followed-up for six weeks. Arrhythmias in some form were found in 16·3 per cent.; of these, extrasystoles were commoner than any other form, the incidence being 7·7 per cent. Sixty-three patients had ventricular extrasystoles, with twenty-three deaths (mortality of 35·6 per cent.) Of these, twenty-six had not received quinidine and ten died (38·4 per cent.), and of the remaining thirty-seven who were given quinidine thirteen died (35 1 per cent). Seven had auricular extrasystoles of whom one died, and one had nodal premature beats. Total. Seventy-one patients of whom twenty-four died (33 8 per cent). These authors think that extrasystoles occur more frequently than these figures would indicate, also that the presence of extrasystoles had a bearing on the mortality rate. This was particularly high in the thirteen patients with ventricular tachycardia of whom eight died (61·5 per cent)

Two rather unusual personal experiences may briefly be mentioned; they are illustrated in Fig 191. Both records were obtained in patients with a recent infarction in the posterior wall The top tracing shows—in addition to the usual features of the ventricular complexes—auricular extrasystoles with aberration of the ventricular portion of the first extrasystole of each series and short paroxysms of auricular fibrillation. The bottom tracing reproduces an unusual monophasic record with numerous ventricular extrasystoles. Both patients survived the attack

In some patients with myocardial infarction the shape of extrasystoles may suggest the diagnosis in the absence of diagnostic features of the sinus beats Some instances are described in the sections on " Ventricular " and " Auricular Extrasystoles " (pp. 31 and 52).

Auricular extrasystoles are more common in infarction of the posterior wall; this is understandable since the sinus node and large portions of the auricles are supplied by the right coronary artery

Abnormalities of the auricular mechanism, including auricular extrasystoles, are also found more frequently in auricular infarction, that of the right auricle being more common than of the left This has been found experimentally as well as clinically (Cushing, Feil, Stanton and Wartman; Schott)

Since the occurrence of extrasystoles in acute myocardial infarction often is a danger signal and more numerous ventricular ones may be the precursors of ventricular tachycardia, with the ominous risk of sudden death from ventricular fibrillation, the routine exhibition of quinidine (*see* p 475) as a preventive has been suggested in all patients with acute myocardial infarction (Morawitz and Hochrein) In a large hospital quinidine in doses of 0 1 gramme twice daily was routinely given to all patients with aortitis and coronary sclerosis and its exhibition continued throughout the patients' stay in the hospital, sometimes for months. This method was claimed successful on the grounds of the following data: in the year before the medication was introduced (1927), twenty-four patients died suddenly, the presumed cause of death being ventricular fibrillation. In the following year 1928, the first during which this method was applied, only five instances of sudden death were observed The total number of patients was about seven thousand a year. The validity of this conclusion seems to us doubtful in view of the long intervals between the exhibition of such small doses of the drug which is eliminated so quickly There is also no experimental evidence that quinidine prevents ventricular fibrillation after coronary ligation However, similar good results were reported by Borg In his series the mortality due to sudden death dropped from twenty-three in 1935 to five in 1936 when the routine exhibition of quinidine (0 2 gramme three times a day) was instituted.

Since in a large proportion of patients with extrasystoles after coronary occlusion the ectopic beats disappear after quinidine medication, it is recommended to give quinidine sulph. 0 15–0·2 gramme every four hours for the first three weeks following the infarction in all cases This is not done universally, but quinidine should certainly be given in every case of coronary occlusion in which extrasystoles occurred (except isolated ones at

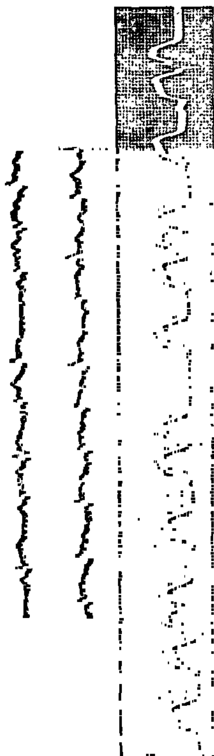


FIG 191 —Both records lead 3 Both from patients with a recent infarction in the posterior wall Top record The two tracings are continuous Auricular extrasystoles with aberration of the ventricular portion of the first extrasystole of each series, also short paroxysms of *auricular fibrillation* *Bottom record* Unusual *monophasic* complexes with numerous ventricular extrasystoles

very long intervals). If necessary for the suppression of the arrhythmia the dose may be increased

Ventricular extrasystoles are often encountered in patients with coronary sclerosis without myocardial infarction or angina pectoris. Not infrequently they are the first manifestation of the disease, particularly in men over forty. They occurred in forty-two instances amongst 974 cases of coronary sclerosis, that is in 5·5 per cent. (Cowan and Ritchie)

In such cases extrasystoles may occur after exertion or immediately after an exercise test (Goldhammer and Scherf), and usually show varying shapes in the electrocardiogram. Since, in subjects without myocardial disease, extrasystoles as a rule disappear during and immediately after exertion, the above observation is of diagnostic importance. In some instances the occurrence of extrasystoles during exertion coincides with the onset of angina of effort and the arrhythmia subsides with the pain (Mathieu; Wayne and Laplace; Proger, Minnich and Magendantz; Porter, 1948)

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Hypertension

The question of the incidence of extrasystoles in hypertension is of interest from various points of view.

For a long time, on experimental grounds a disproportion between the contractile power
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mental aortic stenosis is not infrequently quoted

Clinically, this problem is of interest in view of the very common occurrence of hypertension.

Figures in the literature vary greatly Warkentin reported no effect of raised blood pressure on the incidence of extrasystoles whereas Peel found an incidence of 26 per cent. amongst 184 patients with hypertension The figures of other investigators fall between such extremes, for instance an incidence of 7 per cent found by Koppang, and of 3·5 per cent in eight hundred uncomplicated cases of hypertension by Flaxman In the latter series the immediate mortality of patients with extrasystoles was only slightly higher than the average of the whole series

Wenckebach and Winterberg stressed the difficulties in arriving at accurate figures. gst the total of their cases with extrasystoles 8 per cent. had hypertension. A more re- method seemed to these authors to determine the incidence of extrasystoles in 408 ts with hypertension Of these, 243 had a systolic pressure exceeding 190 mm. Hg venty-six (11·25 per cent.) had extrasystoles; amongst the remaining 165 patients blood pressure of 150–190 the incidence of extrasystoles was eighteen (11·1 per cent) these figures Wenckebach and Winterberg concluded that neither the height of the pressure nor the presence of hypertension *per se* had any significant effect on the nce of extrasystoles This view was supported by the small number—twenty-six—of ts under forty in a series of 385 hypertensives, since in that younger age group the nce of extrasystoles is known to be high.

cording to Fishberg, arrhythmias are common in the failing hypertensive heart and asystoles are, perhaps, the most frequent form of irregularity ". However, this holds also for normal subjects.

ch discrepancies in the findings of the various investigators are not surprising since roblem is complex On the one hand, it is common clinical experience that multitudes pertensives have no arrhythmia On the other, in those exhibiting extrasystoles other s are likely to be of importance Of these, coronary sclerosis takes first place: its ce in a large proportion of middle-aged and elderly hypertensives is most probable. over, the influence of nervous and hormonal factors, discussed in the appropriate ns, is of equal importance Regarding the former, the proneness of many hyperten- to emotional instability needs no stressing Concerning the latter, the appearance of ystoles during a hypertensive crisis in patients with a phaeochromocytoma of the renals (Hegglin and Holzmann) provides an instructive example Here, it seems nable to assume that not the hypertension *per se*, but the circulating pressor amines ephrine and *nor*-epinephrine) are responsible for the arrhythmia

e observation, made more recently by Scherf, Scharf and Goklen, that in certain imental conditions stretching of the auricles may precipitate auricular ectopic beats s to the importance of mechanical stretching in this connexion, but this finding cannot ut reserve be applied to the human heart However, the occurrence of paroxysmal cardia and particularly of auricular fibrillation after unusually heavy exercise has been reported in subjects with normal hearts and it is thus quite possible that acute tion of the heart may precipitate extrasystoles in some cases

SUMMARY

ronic uncomplicated hypertension cannot be considered to favour the occurrence of ystoles Pronounced acute rise in blood pressure seems in some healthy subjects to ectopic beats, the stretching of the cardiac chambers possibly being a precipitating .

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Trauma

Since any slight mechanical stimulation of the heart may cause extrasystoles it is not surprising that they are found in cases of penetrating injury of the heart (stab or gun-shot wounds) and it is very probable that premature beats occur in most cases at the moment of accident

During surgical manipulation of the heart extrasystoles occur frequently, it has been proposed to prevent such arrhythmias by means of procaine (q v) In cases of injury to, or ligation of, a coronary artery extrasystoles are likely to occur for longer periods and constitute a dangerous complication

Non-penetrating injury causing concussion and contusion of the heart may also cause extrasystoles. Blunt trauma to the chest wall, particularly to the praecordial region, may produce an area of myocardial necrosis which, just as in cases of myocardial infarction, after a short time sets up an inflammatory reaction Moreover, haemorrhages occur in all layers of the heart In these circumstances extrasystoles were seen clinically as well as experimentally

Clinical Observations. Since a considerable number of clinical instances had been reported before this problem was first investigated experimentally in detail, the clinical aspect is discussed first.

Amongst ninety cases of non-penetrating injury to the heart Warburg (1938) encountered extrasystoles in nine instances, and in a subsequent series of fifty-nine cases, in two (Warburg, 1940) Similar findings were published by others (Kahn, Barber) Such statistical data are, however, to be used with reserve, for the presence of extrasystoles occurring independently of trauma has to be considered, moreover, in those instances in which extrasystoles developed as the result of trauma, they may well be absent during the short period of examination or may have already disappeared by that time In one case, reported by Hyman and Fisher, left-ventricular extrasystoles were observed post-operatively after a stab wound in the base of the left ventricle In Baledent and Bizard's case the extrasystoles had an unexpected shape in the electrocardiogram, considering the site of the traumatic lesion

Experimental Investigations. Moritz and Atkins produced blunt cardiac trauma in thirty-two dogs; extrasystoles were observed in five The anatomical examination showed local contusion in two animals and failed to reveal any injury in the remaining three Others (Kulbs, Schlomka and Hinrichs, Beck, Bright and Beck) also observed extrasystoles following blows applied directly to the exposed heart and those to the intact chest wall

Similar findings were obtained by Scherf and Terranova from whose experiments Figs 192 and 193 are taken

Fig 192 was obtained from a cat By means of a guillotine-like device a weight of 2 kg. was made to fall on the praecordial area from a height of 100 cm A ventricular tachycardia appeared immediately after the trauma This was followed by ventricular extrasystoles which had the same shape as the abnormal beats during the preceding tachycardia and which often occurred as coupled beats In other experiments auricular extrasystoles occurred immediately after the trauma (Fig 193) Such arrhythmias as well as auricular fibrillation, which was commonly observed in such experiments, disappeared within a few minutes The experiments were not carried out sufficiently long for studying the possible re-appearance of the ectopic beats, this might well be expected in view of the reactive changes in the injured tissue, discussed above

Regarding the mechanism underlying such arrhythmias, Schlomka and Hinrichs ascribed them to vasospasm consequent upon the trauma In our opinion it is far more likely that they were due to the mechanical stimulus and damage of the trauma The arrhythmia—as well as changes in the final deflections—occurred instantaneously after the trauma and the interval is thus too short as for vasospasm to account for the disturbance

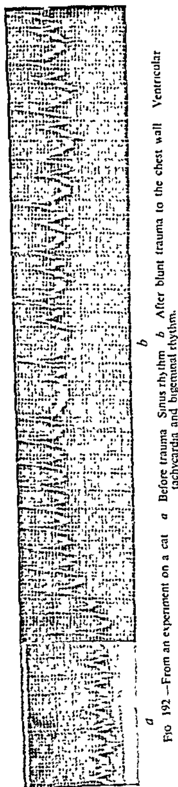


FIG 192.—From an experiment on a cat *a* Before trauma Sinus rhythm *b* After blunt trauma to the chest wall Ventricular tachycardia and bigeminal rhythm.

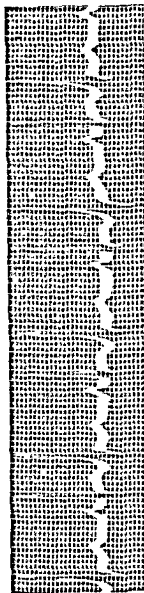


FIG 193.—From an experiment on a cat. Auricular bigeminy after blunt trauma to the chest wall.

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Catheterization

With the increasing use made of catheterization of the heart, disorders of cardiac action elicited by this procedure are assuming great clinical importance Amongst these, ectopic arrhythmias are frequent and their study is also of considerable physiological interest It has, of course, been known for a very long time that experimentally even slight mechanical stimulation of the epicardial and particularly of the endocardial surface elicits abnormal contractions

Extrasystoles were reported soon after catheterization was employed more widely Bloomfield *et al* found ventricular ectopic beats frequently in seventy-seven catheterizations on seventy subjects and considered the arrhythmia probably due to contact of the tip of the catheter with the heart. Sosman encountered extrasystoles in about one-half of a hundred cases when the catheter was passing through the tricuspid orifice Dexter *et al.* reported cardiac irregularities during catheterization in twenty-seven out of forty-two patients, demonstrated by electrocardiogram, pulse tracings or palpation, and ventricular extrasystoles in five out of twelve patients with repeated electrocardiograms In a later study (Levine *et al*, *see* below) it was found that the incidence of ventricular extrasystoles actually is considerably higher than this early study seemed to indicate

In an early paper [illegible] cavity leads, emphasized the similarity in shape of right ventricular extrasystoles in the right auricular electroendocardiogram and the right precordial leads, also lead aVR; left ventricular extrasystoles, which occurred during catheterization, showed an initial upstroke in leads obtained from the right auricle and right ventricle The bearing which the findings of these authors have on the localization of the focus of origin of ectopic beats is discussed in the appropriate chapter (p 399) In the right auricular cavity record of auricular extrasystoles their P waves started without the initial upstroke of the P waves of sinus beats, which was interpreted as indicating a focus of origin of such extrasystoles beneath the exploring electrode in the right auricle

Levine *et al.*, employing intracavity leads, emphasized the relative rarity of auricular [illegible] they were precipitated by the catheter With the catheter in the right ventricle, on the other

hand, ventricular premature beats or paroxysms of ventricular tachycardia occurred in the "vast majority" of the series of twenty-seven cases. Such arrhythmias invariably disappeared when the tip of the catheter was advanced into the pulmonary artery or withdrawn into the right auricle These authors assume that the ectopic beats were due to contact of the tip of the catheter with the right ventricular endocardium of the interventricular septum The reason for the more frequent occurrence of ventricular, as compared with auricular ectopic beats is believed by these authors to be that, in the auricle, the intracardiac electrode is more prone to remain in midstream and therefore not placed in a position favourable for precipitating extrasystoles by being in intermittent contact with the wall of the chamber, as is the case in the ventricle We should like to add as another probable reason that specialized tissue is present throughout the ventricles whereas in the auricles it is limited to the S-A and A-V nodes Some further details about the electrocardiographic appearance of such ectopic beats are discussed on p 399

Some impression of the incidence of such arrhythmias in connexion with cardiac catheterization may be conveyed by Table 4 (p 433)

In the series of 133 catheterized patients of Michel *et al.* the incidence of arrhythmias was found twice as high in patients with congenital heart disease as in the remaining group of acquired (mostly hypertensive and coronary) cardiac lesions; it was also significantly higher in patients with pre-existing electrocardiographic abnormalities

A few individual points may be briefly mentioned

The predominence of ventricular over auricular ectopic beats is mentioned by most investigators, for example Levine *et al*, Goldman *et al*, Landtman, Ravin *et al*, Michel *et al* Most authors also express the opinion that the ectopic beats are elicited mechanically by the contact of the tip of the catheter with the endocardial wall. However, the various portions of the heart vary in their propensity to develop ectopic rhythms.

In the electrocardiographic study in connexion with angiocardiography of Biorck *et al*, premature beats occurred in all twenty-one cases injected by a catheter into the right auricle, right ventricle or pulmonary artery whereas none were observed in the cases in which the injection was given into the superior vena cava (three) or in the aorta (twenty-two) Landtman found that such arrhythmias were elicited most readily from the infundibulum of the right ventricle, the area near the tricuspid valve and the remaining part of the right ventricle whereas they occurred far less frequently from the stem or branches of the pulmonary artery or the right auricle The focus of origin was assumed to be the subendocardial specialized system, particularly the peripheral ramifications (Landtman)

The relationship between the mechanical stimulus provided by the catheter and the ensuing arrhythmias seems, however, to be more complex Ravin *et al.* pointed out that ectopic beats elicited from the septum may vary in shape and timing, and expressed the opinion that such arrhythmias originated from multiple irritable foci. Similar observations were made by Landtman when the tip of the catheter touched the infundibulum. (Regarding the determination of the site of origin of ectopic beats generally, as mentioned in some of the discussed papers, some doubts may be expressed about the validity in those instances in which this was based on the shape of the ectopic beats in only one standard or praecordial lead)

Biorck *et al* remarked that the localization of the tip of the catheter did not seem to decide the type of the premature beats ventricular extrasystoles were seen when the contrast medium was injected into the auricle, and auricular premature beats with injection into ventricle or pulmonary artery While these authors assume most electrocardiographic disturbances to be due to some direct mechanical intra-cardiac irritation, either by the catheter or the spout of the injected medium, "the possibility of an indirect influence of cerebral and nervous factors will also have to be taken into account".

Similar observations were made by Michel *et al*, who found in a considerable proportion of their 133 catheterized patients that "intra-auricular locations of the catheter tip

were associated with a variety of extra-auricular rhythms It appeared difficult to explain the mechanism of impulse origin in these instances except on a basis of reflex excitation of the endocardial or endothelial surface other than the point of impulse formation." This view was supported by observations on serious arrhythmias occurring before the inserted catheter had been advanced into the superior vena cava or past the axilla, or, in one fatal case, even immediately following its introduction into the vein

The importance of nervous factors in the causation of ectopic arrhythmias is discussed in the appropriate chapter (p 253). Furthermore, such observations recall the experimental findings of Scherf *et al* that, in certain circumstances, activity of one ventricular ectopic centre may stimulate impulse formation in other ectopic foci.

Another form of a possible stimulation of an ectopic focus was seen by Kossmann *et al*, using an intracavitary lead. This group of workers observed the temporary occurrence in the electrocardiogram of complexes closely resembling pre-excitation which they considered due to a temporary increase in excitability of a ventricular centre by the catheter They were led to favour a functional rather than structural explanation of this phenomenon (W P.W. syndrome), a conjecture at which Coelho *et al* also arrived as a result of similar experimental and clinical observations. We do not agree with this view for reasons discussed in the next section (*q.v*, p. 438).

In thirteen of the eighty-eight children with arrhythmias of Landtman's series the tip of the catheter reached the left heart, in most of these cases through an inter-atrial septal defect, and of the fifteen instances of disturbances of rhythm extrasystoles were the commonest Auricular tachycardia was observed in a young child with an inter-atrial septal defect when the catheter passed through it (Johnson *et al*)

An unusual observation was made by Ravin *et al.* on a patient with spontaneous attacks of auricular paroxysmal tachycardia when, during such an attack, the catheter entered the right ventricle, a ventricular tachycardia was precipitated which subsequently changed into sinus rhythm, a truly "unique method of stopping a paroxysmal tachycardia" Zimdahl reported in a girl of four with an interventricular septal defect an instance of lower nodal tachycardia elicited by the catheter, which persisted after the catheter was withdrawn into the superior vena cava and was terminated after thirty minutes by procaine His paper contains a useful summary of experimental and clinical observations on the various disorders of the cardiovascular system during catheterization

In the majority of instances ectopic arrhythmias cease when the location of the catheter is altered or, if necessary, withdrawn In some cases the exhibition of drugs proved necessary, of which procaine, quinidine and atropine have been successfully employed. Procaine amide (Pronestyl), which has recently been introduced in the treatment of—especially ventricular—ectopic arrhythmias, may prove useful in some instances of this kind though we are not aware of any reports yet published on the use of this drug in connexion with cardiac catheterization except in one case in the series of Lasser *et al.* (*see also* section on "Cocaine", p 309)

Considering how widely catheterization is employed, fatal ectopic arrhythmias caused by it have been reported in only a small number of cases. Nevertheless they are of great clinical significance since they call for immediate change of position or withdrawal of the catheter, supplemented in some cases by the administration of drugs; they have to be regarded as potentially ominous precursors of fatal ventricular fibrillation

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Extrasystoles and Pre-excitation Syndrome

The " pre-excitation " or " Wolff-Parkinson-White " (WPW) syndrome is characterized in the electrocardiogram by abnormally short P-R intervals followed by QRS complexes of abnormal shape and increased width The latter indicate anomalous intraventricular conduction

The syndrome is now generally accepted as being due to the conduction of the S-A impulse to the ventricles by an abnormal pathway, namely an accessory A-V connexion

The condition is often found in otherwise normal subjects Numerous instances were published as a result of electrocardiograms taken during the war in service personnel without any evidence of structural heart disease Grave and even fatal cases showing this syndrome have, however, been reported (Broustet *et al*)

The frequent occurrence in this condition of attacks of paroxysmal tachycardia is universally recognized Scherf and Schönbrunner found a history of such attacks in twenty out of thirty-five cases with this type of electrocardiogram In his comprehensive paper on the pre-excitation syndrome Oehnell reported paroxysmal tachycardia in 70 per cent. of a large number of cases collected from the world literature. Schott described this association in an infant of eight months

Auricular and ventricular extrasystoles also occur in the WPW syndrome, but, as distinct from the association with paroxysmal tachycardia, only comparatively few cases have been published (Scherf and Schonbrunner, Littmann and Tarnower)

Fig. 194 was obtained from a forty-six-year-old man who stated to have always been healthy except for occasional attacks of palpitation. Examination revealed a WPW syndrome which disappeared after exercise (*see* Scherf and Schonbrunner) Fig. 194a shows

TABLE 4

Ectopic arrhythmias observed in connexion with cardiac catheterization

No of Cases	Extrasystoles						Tachycardia						Remarks	Author
	Auricular		Nodal		Ventricular		Auricular		Nodal		Ventricular			
	No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent		
23	17	74	8	35	20	87	2	8.7	—	—	—	—	Twenty-two patients had tuberculosis, one asthma	Ravin *et al*
50	30	60	39	78	44	88	7	14	9	18	39	78	Thirty-six had congenital heart disease All patients showing auricular or nodal tachycardia had congenital heart disease Ventricular tachycardia diagnosed when more than 3 ventricular extrasystoles occurred in succession Auricular flutter in 3 patients, auricular fibrillation in none	Goldman *et al*
142	31	22 (36)	7	5 (8)	69	49 (79)	2	1.4 (2.2)	—	—	22	15 (25)	All children One hundred and sixty cardiac disturbances observed in 88 of the 142 The percentage incidence of the listed arrhythmias amongst these 88 is given in parenthesis	Landtman
133	3	4	—	—	35	55	2	3	—	—	14	22	The figures refer to numbers and percentage of incidence from Table 2 of original	Michel *et al*
49	7	14	11	22	33	66	6	12	—	—	12	24	Forty-three records from patients with congenital heart disease, 4 normals, 2 with rheumatic valvulitis Ventricular tachycardia defined as runs of 3 or more ventricular extrasystoles	Lasser *et al*

the typical features of the WPW syndrome with an auricular extrasystole following every or every second sinus beat. The P waves of the extrasystoles are visible in the T waves of the preceding beat. Fig 194b also shows auricular extrasystoles: one occurred after the

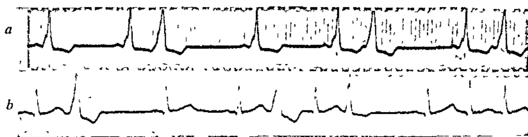


FIG 194—*a* and *b* from the same patient Pre-excitation syndrome with auricular extrasystoles For explanation, see text From SCHERF and SCHONBRUNNER *Z klin Med*

first normal sinus beat, the third sinus beat is followed by three auricular extrasystoles, and another two are seen at the end of the tracing These extrasystoles show three kinds of QRS complexes some resemble those of the normally conducted sinus beats, others are very similar to those of the sinus beats with anomalous intraventricular conduction, and others again, for instance the last of the three extrasystoles following the third sinus beat, have an intermediate shape The assumption seems justified that some of these premature beats were normally conducted through the A-V bundle, some of them through an accessory bundle, and some simultaneously over both pathways An interesting observation in this



FIG 195—*a* The three standard leads Pre-excitation syndrome during normal rhythm

case was that exercise improved the conduction in the A-V bundle not only for the sinus beats, but also for the extrasystoles

Fig 195 was obtained from a fifty-eight-year-old man complaining of attacks of

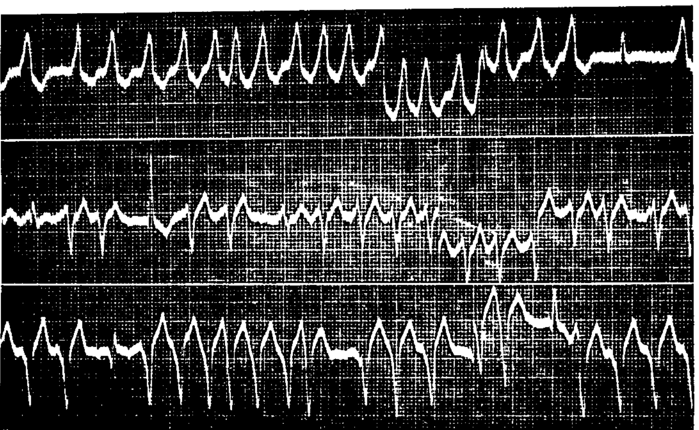


FIG 195 — *b* From the same patient as Fig 195—*a* The 3 standard leads During an attack of auricular fibrillation For further explanation, see text

palpitation lasting from a few minutes to several hours. The tracings reproduced in Fig. 195a indicate the WPW syndrome, in lead 1 the characteristic broad slurring in the ascending limb of the R waves is easily recognized. Fig. 195b was obtained from the same patient during an attack of auricular fibrillation It is evident that most of the beats show anomalous intraventricular conduction, though a few (the penultimate in lead 1, the fourth in lead 2 and two in lead 3) have ventricular complexes indicating normal A-V conduction, but are otherwise abnormal due to myocardial damage caused by coronary sclerosis Those beats which show evidence of being conducted through an accessory pathway have continually varying form of the QRS complexes, the width of which varies between 0·10 and 0·14 second Combination beats also occurred. The assumption follows that both the normal A-V and *the accessory bundle were functioning and that some of the impulses reached the ventricle* through both pathways

Recognition of this syndrome is also important because of the possible confusion in some cases with extrasystoles Fig. 196 provides an example. It shows sinus rhythm whereby every other beat shows the pre-excitation syndrome Casual inspection may suggest bigeminal rhythm with ventricular extrasystoles occurring late in diastole, whereas the correct explanation is regular sinus rhythm with alternation of ventricular excitation between normal and anomalous intraventricular conduction (*see also* chapter on "Coupling", Fig. 136)

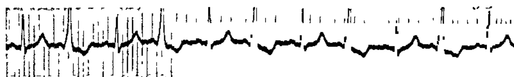


Fig 196—Sinus rhythm with every other beat showing the pre-excitation syndrome See text

Underlying Mechanism

The most generally accepted explanation of the syndrome of shortened P-R intervals with anomalous intraventricular conduction is that put forward by Holzmann and Scherf in 1932 and Wolferth and Wood in 1933 According to this view the impulse originates normally in the S-A node, but is conducted to the ventricles by an abnormal pathway, particularly, but not invariably, the right lateral bundle, described by Kent in 1892 and often called the "bundle of Kent" Several such connexions have been described and some of them were found in patients who had shown the WPW syndrome (for instance Wood, Wolferth and Geckeler; Oehnell) Scherf and Schönbrunner pointed out the phylogenetic significance of such accessory pathways as remnants in man of the more numerous and broader connexions found in lower animals

Numerous other explanations were put forward at different times by different investigators; they are listed in the paper by Hunter *et al* Of these, Holzmann and Scherf considered, but rejected, the assumption of an irritable focus in the ventricle which, in such cases, is stimulated mechanically by each auricular contraction This view has recently been tentatively put forward again by Kossmann *et al.* In recording intracavitary leads, these authors found the temporary occurrence of "pre-excitation" complexes on slowly [illegible] procedure created [illegible] which was stimu- [illegible] ntricular pressure which it causes They thus suggest tentatively a functional rather than an anatomical

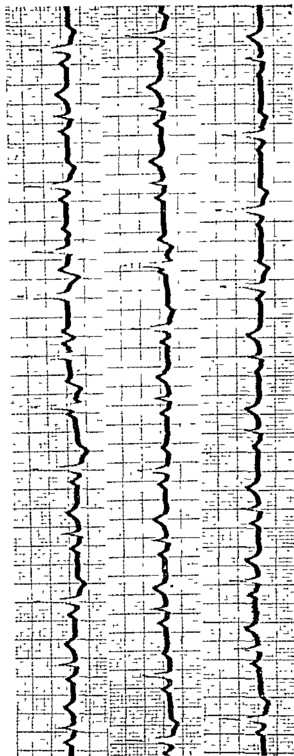


FIG 197.—Arrhythmia recorded during cardiac catheterization in a forty-two-year-old man with congenital pulmonary stenosis Ventricular ectopic beats at times simulating " *pre-excitation complexes* " *The three strips are continuous* For further explanation, see text

explanation of this syndrome Coelho *et al* arrived at similar views as a result of clinical and experimental observations.

While on the grounds of personal observations we can confirm the occurrence of "pre-excitation complexes" during cardiac catheterization (*see* Fig. 197), we do not believe that this indicates the creation of an irritable focus in the ventricles activated by auricular contraction, but consider such beats to be ventricular ectopic beats, elicited by the catheter, the timing of which results in the fortuitous appearance of pre-excitation complexes. Such timing is the more easily understandable as some varieties of ectopic ventricular rhythms are known to have rates very similar to that of the prevailing sinus rate. For instance, the rates of ectopic ventricular rhythms elicited in dogs by mechanical stimuli parallel those of the sinus rhythm in the individual case (Scherf, 1926), and a similar parallelism between ectopic and sinus rates was demonstrated in experimental parasystole (Scherf and Chick) (Comparable conditions were found by Luten in a case with auricular extrasystoles, discussed on p 260) Moreover, more recent observations in two cases have shown unquestionable disturbances of atrio-ventricular conduction in the presence of the pre-excitation syndrome which, in our opinion, proves that this phenomenon is in fact due to anomalous conduction (Scherf, Blumenfeld and Mueller).

An interesting problem is the high incidence of paroxysmal tachycardia in such cases Hunter *et al* found the WPW syndrome in 5 per cent. of 150 consecutive patients with paroxysmal tachycardia, other figures were given earlier in this section. The association is certainly not fortuitous and requires an explanation

One theory goes back to the hypothesis of Mines (1914) and de Boer (1927), put forward at a time when the pre-excitation syndrome was not yet recognized; this seeks to explain extrasystoles and paroxysmal tachycardia as due to a circus movement involving the A-V conduction system and the bundle of Kent According to this view the impulse is conducted through the A-V system from the auricles to ventricles and thence back to the auricles through the bundle of Kent A circus movement through this pathway was assumed to underlie supraventricular tachycardia Circulation of the excitation in the reverse direction through the same paths was thought to precipitate ventricular tachycardia. It is true that in experiments on dogs and cats Butterworth and Poindexter were able to produce paroxysmal tachycardia by stimulating the auricle by means of the amplified ventricular action current However, the objection to this explanation is that sharply inverted P waves should be found between two ventricular complexes in leads 2 and 3 and no such instance has so far been published Moreover, the observation that in a case of WPW syndrome during auricular paroxysmal tachycardia the excitation was found to use either pathway at different times is not in accordance with the assumption of a circus movement (Scherf and Boyd).

Another explanation seems more plausible, put forward by Scherf (1950) It is based on the observation that an excitation activating the heart late in systole or early in diastole, that is, during the "critical" or "vulnerable" phase, may precipitate a series of contractions, a repetitive response, instead of one single contraction (*see* p. 483) It seems possible that in patients with the pre-excitation syndrome the excitation, which reached the ventricle through one pathway, arrives by the other pathway in the auricle during its critical phase and, in this way, causes a repetitive response in the form of paroxysmal tachycardia or auricular fibrillation

SUMMARY

The Wolff-Parkinson-White, or pre-excitation syndrome is characterized in the electrocardiogram by abnormally short P-R intervals and anomalous intraventricular conduction. In this condition extrasystoles are commoner than the few published examples may suggest. Several instances are given and illustrated.

Activation of the ventricles by an accessory A-V connexion is the explanation most

generally accepted. A functional explanation—previously rejected—based on the assumption of an irritable focus in a ventricle which is activated by the auricular contraction, has recently again been put forward on the grounds of observations made during the recording of intracavitary leads. Reasons are given why we consider this view to be unacceptable.

The difficulties in the differential diagnosis, in some cases, between the WPW syndrome and ventricular extrasystoles are emphasized

The association of the WPW syndrome with paroxysmal tachycardia is universally recognized. The explanation is put forward that this may be due to the return of the impulse from the ventricles to the auricles during the vulnerable phase of late systole or early diastole of the auricles, thereby resulting in repetitive response

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EXTRASYSTOLES IN RELATION TO VARIOUS TYPES OF EXTRACARDIAC CONDITIONS

Cheyne-Stokes

In patients with Cheyne-Stokes breathing arrhythmias of various kinds are sometimes observed, amongst them extrasystoles which periodically occur only during certain phases of this periodic type of respiration

In two digitalized patients, extrasystoles were noted during the hyperpnoeic phase (Roth).

In Fischer's case ventricular extrasystoles occurred at the end of hyperpnoea, and Wassermann reported tachycardias with ventricular extrasystoles during apnoea. Extrasystoles occurring during certain phases of the respiratory cycle were also reported by Wenckebach and Winterberg, and by Hoesslin.

Fig 198 was obtained from a sixty-seven-year-old woman with marked Cheyne-Stokes breathing; she had not received digitalis. On clinical examination tachycardia was noticed during the apnoeic periods which the electrocardiogram revealed to be an ectopic ventricular tachycardia, starting soon after the beginning of apnoea and extending into the beginning of the hyperpnoeic phase Alternation of the ventricular complexes was often seen during the ventricular tachycardia (*see* top tracing, Fig 198).

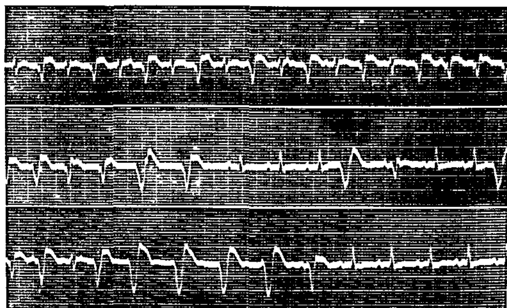


FIG [illegible] [illegible] various phases of [illegible] dia starting soon [illegible] ricular complexes [illegible]

Regarding the underlying mechanism of such periodically recurring arrhythmias, the periodical changes in the gaseous composition of the blood seem to be the most important factor It may be recalled that a rise in the carbon dioxide content of the blood inhibits the formation of extrasystoles (Scherf, Goldenberg and Rothberger) and may transform an ectopic tachycardia into single extrasystoles (*see* sections on " Coronary Disease " and on " Digitalis ") This aspect was studied by Steele and Anthony in respect of Cheyne-Stokes respiration As expected, the lowest concentration of O_2 was found during the early stages of the hyperpnoeic phase, the highest at the end of hyperpnoea or beginning of apnoea, regarding the concentration of CO_2 the reverse changes were observed. The patient investigated by these authors showed arrhythmias of various kinds, including paroxysmal tachycardia, during apnoea, and varyform ventricular extrasystoles at the transition from apnoea to dyspnoea

In addition to changes in the gaseous composition of the blood, those in rate and in nervous tone seem important contributory factors.

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Hyperventilation

As far as we are aware the effect, upon ectopic impulse formation, of hyperventilation and alcalosis has not been investigated One personal observation may briefly be discussed in which hyperventilation was repeatedly followed by a conspicuous reduction in the number of ectopic beats.

The patient in question was kept under observation for many years and electrocardiograms invariably showed long paroxysms of ectopic auricular tachycardia As the P waves were inverted in leads 2 and 3 the abnormal beats presumably originated in the vicinity of

rhythm ensued with marked aberration of intraventricular conduction (Fig 199d) A few minutes after the termination of hyperventilation the arrhythmia reverted to the original ectopic tachycardia as reproduced in Fig 199a In this particular patient bi- or trigeminal rhythms were never observed except after hyperventilation

X-ray Irradiation

In view of the profound effect of X-rays on living tissue some influence on ectopic impulse formation is only to be expected, but in actual clinical experience is far less common than anticipated

In 1897 Segny and Quenisset reported intolerable palpitation and irregular contractions as a result of "very long" X-ray irradiation Some arrhythmias, not further analysed, were reported by Coutard and Lavedan, in these, extrasystoles may have played a part

(Hartman *et al*, Warthin and Pohle, Werthemann, Desjardins), also the clinical observation of pericarditis resulting from this interference (Leach, 1943a) Greater resistance, to the damaging effect of the X-rays, of the heart than of the lungs was claimed by Desjardins, and it

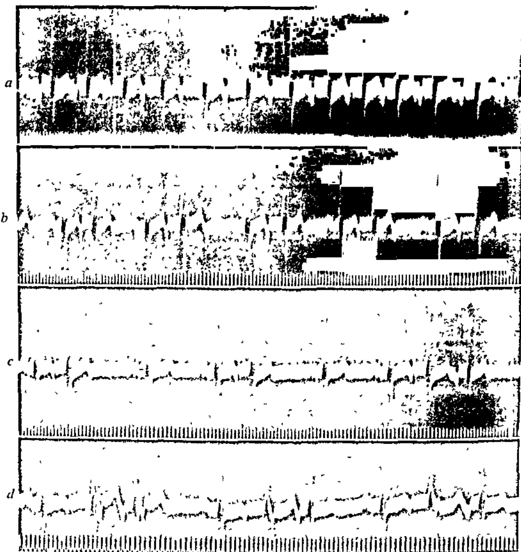


FIG 199—Lead 2 *a* Before hyperventilation Ectopic tachycardia, presumably originating in the vicinity of the coronary sinus Note sharply inverted P waves *b*, *c* and *d* after five minutes hyperventilation *b* Bigeminal rhythm, *c* Two normal beats followed by an auricular extrasystole Two auricular extrasystoles in succession at the end of this strip, *d* Auricular trigeminy with aberrant intra-ventricular conduction of the extrasystoles Time base: 0 04 second

is noteworthy how often irradiation with large doses is given for mediastinal tumour without much clinical evidence of myocardial damage In the electrocardiogram signs of myocardial damage are by no means rare and gallop rhythm may appear in such circumstances (unpublished personal observations), these features have to be ascribed to the X-ray treatment

(Gendreau claimed to have found "far-reaching" effects of X-rays on the heart, but his electrocardiograms show only artifacts)

Regarding extrasystoles, our personal experience is limited to one case. It concerned a patient with short paroxysms of auricular tachycardia which were separated by only one sinus beat (extrasystolie à paroxysmes tachycardiques, p. 237) (Fig 200a) This arrhythmia was invariably recorded during a period of observation extending over many years About four hours after irradiation of the praecordial region with 100R the arrhythmia reproduced in Fig 200b was found · the chains of ectopic beats had become shorter and two sinus beats followed in succession; the last of the auricular ectopic beats was blocked The same effect upon the arrhythmia was repeatedly observed, also when other parts of the body were irradiated. It seems reasonable to conclude that this change in the arrhythmia was due, not to any direct effect upon the heart, but to an indirect effect consisting, most probably, in a metabolic change resulting from the irradiation

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Hyper- and Hypothyroidism

Hyperthyroidism

In view of the common occurrence, in hyperthyroidism, of auricular fibrillation it is surprising that extrasystoles are comparatively rare (Wilson) This is the more remarkable since in other conditions predisposing to auricular fibrillation (coronary disease, mitral stenosis) auricular extrasystoles are found so often as precursors The increased heart rate was considered to be one factor to account for the comparative rarity of extrasystoles in this condition (Bickel and Frommel, Wishart) and, if extrasystoles were found in such cases in spite of a high heart rate, they were thought to indicate myocardial damage (Boas and Levy) Towers considered the occurrence of extrasystoles in the presence of sinus tachycardia as typical for hyperthyroidism How infrequent extrasystoles are in hyperthyroidism may be illustrated by recalling Goodall's review of the heart in Graves' disease, in which 7 per cent of the patients were found to have auricular fibrillation and extrasystoles were not mentioned at all Similar findings were reported by Willius

On the other hand five instances of ventricular and three of auricular extrasystoles were encountered amongst 188 patients with hyperthyroidism (Parade) and Van de Velde especially stressed an incidence of 4 per cent in his series of five hundred cases Other studies include those of Bickel and Frommel (three instances amongst eighty cases) and of Krumbhaar (three amongst forty-seven) It appears that ventricular extrasystoles are commoner than auricular ones (Nicholson)—another surprising observation This is also borne out

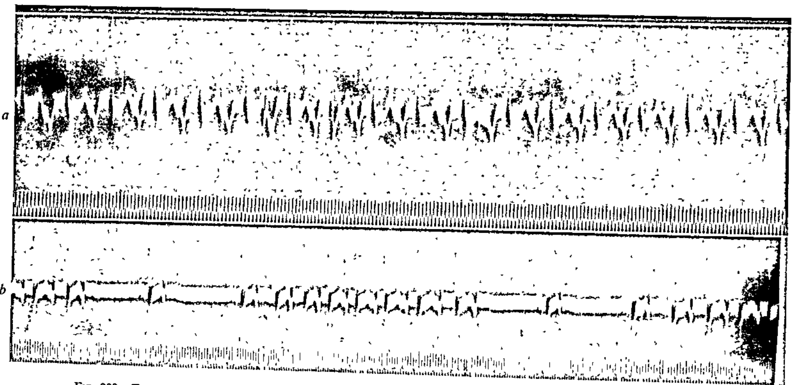


FIG. 200.—Top record: Before irradiation. Paroxysmal auricular tachycardia. The paroxysms are fairly long and separated by only one sinus beat. (Extrasystolie à paroxysmes tachycardiques.) Bottom record: Four hours after irradiation of the precordial region with 100 R. Shorter paroxysms of ectopic tachycardia, two sinus beats in succession, blocked auricular extrasystoles. Time base 0·04 second.

by the figures of Spang and Korth. of the twenty-four patients with extrasystoles amongst two hundred cases of hyperthyroidism, fifteen had ventricular and one ventricular and auricular ones.

Experimental investigations do not seem to throw any light on this problem Bickel and Frommel observed ventricular extrasystoles in rabbits which had been injected with extracts of thyroid glands of sheep But since such ectopic beats occurred very soon after the injection, sometimes within a few seconds, and in any case rabbits are very prone to exhibit such arrhythmias, this observation is of doubtful value.

It has to be admitted that neither the rarity of extrasystoles nor their predominantly ventricular origin is understood As the reason for the frequent occurrence, in hyperthyroidism, of auricular fibrillation is not clear this is hardly surprising There can be no doubt that the association between auricular fibrillation and hyperthyroidism is more than fortuitous Increased sympathetic tone has been thought to be responsible for this connexion, but this is far from certain On the contrary, there is some evidence that increase in parasympathetic tone may play a part administration of choline preparations to patients with hyperthyroidism causes auricular fibrillation more readily than that to normal subjects (Nahum and Hoff). There is also evidence of a direct action of the thyroid hormone on the heart muscle fibres

Hypothyroidism

In our experience the occurrence of extrasystoles in patients with hypothyroidism is not rare, but it seems doubtful whether this clinical condition predisposes to extrasystoles In ong-standing cases they are caused by the associated coronary sclerosis

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Extrasystoles and Different Phases of Sexual Life in Women

The relationship between the occurrence of extrasystoles and the different phases in the sexual life of women has been noticed for a very long time In the pre-electrocardiographic era the " utero-ovarian " arrhythmias were a well-recognized group of irregular heart action Early such arrhythmias attracted attention particularly amongst French clinicians who were inclined to attribute them to reflexes (Leconte, Marchal and Heim de Balsac; Gallavardin).

While such reflexes may perhaps play a part in some cases, it is certain that endocrine factors are usually responsible With increasing endocrinological knowledge it became realized that imbalance between the various endocrine glands, rather than ovarian hypo- or hyper-function, had to be considered as the main underlying factor, acting most probably via alteration of the electrolyte balance

The greater incidence of extrasystoles in women, as found in some statistics (*see* section on " Incidence "), was attributed to arrhythmias of such etiology (Savini).

Pregnancy predisposes to extrasystoles to such an extent that not infrequently this is the only time in a patient's life when they occur (Mackenzie, 1902) and it has been estimated that as many as 50 per cent of pregnant women show extrasystoles (Mackenzie, 1921) As a rule they occur during the later months of pregnancy, about the eighth month, and disappear within a few hours after delivery (Mosler and Sachs, Goodall, Schubert, Jensen, Abraham, Hoskin) Origin by way of reflex is also likely to be an important factor But great variations are found in different cases and in some women who develop extrasystoles only during menstruation they may be absent throughout the whole of pregnancy. In others, paroxysmal tachycardia is observed during pregnancy (Weyler and Dustin). Anderson (1933) followed up a patient during successive gestations and found that, during the first three pregnancies, no attacks occurred; three attacks of paroxysmal tachycardia were seen during the fourth, one during the fifth (in the eighth month), three in the sixth, and more numerous ones during the seventh pregnancy when they started already in the course of the fifth month, no attacks were seen between the pregnancies An unusual observation was reported by McMillan and Bellet, namely, attacks of ventricular paroxysmal tachycardia occurring during pregnancy for the first time and persisting afterwards

The treatment of extrasystoles occurring during pregnancy—which may be very troublesome—presents a special difficulty, since small doses of quinidine often are ineffective and large ones contra-indicated Fortunately, reassurance about the harmless and transient nature of the arrhythmia often is all that is required.

Menstruation, Menopause and Puberty

Ectopic arrhythmias may occur only during menstruation (Crawford, Sigler and Fruchter) or just before it In others, extrasystoles and paroxysmal tachycardia were recorded during the menopause (Hoffmann, Peel, Anderson, 1932). In such cases it is often impossible to be certain whether extrasystoles had not existed before and were only noticed by the patients during the menopause when the change in their general condition makes patients more prone to notice such disturbances of rhythm

Disappearance of extrasystoles with the onset of puberty has also been reported (Anderson, 1933)

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Allergy

Experimental Investigations

In dogs, made anaphylactic by the intravenous injection of horse serum, extrasystoles were not observed though heart block occurred (Auer and Robinson) In rabbits, on the

paid to such observations in rabbits since, as mentioned repeatedly, rabbits develop extrasystoles very readily in a great variety of experimental conditions In guinea pigs extrasystoles were seen during attacks of bronchial asthma experimentally produced (Ewert and Kallos) According to Criep, arrhythmias seen in rabbits and guinea pigs during anaphylactic conditions are due to the concomitant asphyxia, since artificial asphyxia produced the same kind of arrhythmias as did anaphylaxis

Clinical Observations

Extrasystolic arrhythmias were reported in patients allergic to a great variety of agents sweet food (Luria and Wilensky), cold (Duke), a variety of foodstuffs (Weill, Lapeyre, Harkavy, Pantolini) Such arrhythmias included single extrasystoles and paroxysms of ventricular tachycardia In view of the profound tissue—in particular vascular—changes caused by allergy the occurrence of extrasystoles in such conditions is easily understood

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Emotional Factors

Changes of the pulse due to emotions were known to Galen. The following charming anecdote, of which Avicenna (980–1037), the famous Arabian physician, is the hero, may be quoted from E G Browne's Fitzpatrick Lectures

"When in his flight from Mahmúd of Ghazna he came incognito to Jurján or Gurgán (the ancient Hyrcania) by the Caspian Sea, a relative of the ruler of that province lay sick of a malady which baffled all the local doctors. Avicenna, though his identity was then unknown, was invited to give his opinion, and, after examining the patient, requested the collaboration of someone who knew all the districts and towns of the province, and who repeated their names while Avicenna kept his finger on the patient's pulse. At the mention of a certain town he felt a flutter in the pulse. 'Now', said he, 'I need someone who knows all the houses, streets, and quarters of this town' Again when a certain street was mentioned the same phenomenon was repeated, and once again when the names of the inhabitants of a certain household were enumerated Then Avicenna said. 'It is finished. This lad is in love with such-and-such a girl who lives in such-and-such a house, in such-and-such a street, in such-and-such a quarter of such-and-such a town, and the girl's face is the patient's cure' So the marriage was solemnized at a fortunate hour chosen by Avicenna, and thus the cure was completed"

The list of emotions reported to cause extrasystoles is long It includes anxiety, fear, fright, hate, to quote a few (Webber, Lockwood, Bickel, Katz *et al*), domestic or professional troubles, disappointment, feeling of guilt or shame and fear of organic heart disease (Wenckebach and Winterberg, p 242)

Fleisch recorded extrasystoles in two-thirds of subjects investigated during an examination, and Miller and McLean described four instances of extrasystoles occurring during severe inner conflicts Gallavardin and particularly Hoffmann reported attacks of paroxysmal tachycardia regularly elicited by emotion, and Ken Kuré saw multiple extrasystoles and tachycardias in a patient whenever he was asked to solve simple mathematical problems.

That emotions may precipitate extrasystoles becomes understandable if the effect of epinephrine and acetylcholine and the part played by the hypothalamic centres and by autonomic nerves and reflexes is recalled, these are discussed in the appropriate chapters

In view of the fact that premature contractions occurring during a certain period in early diastole (the critical or vulnerable period, *see* p 483) may initiate ventricular fibrillation, sudden death caused by sudden great fright becomes understandable, some instances are briefly discussed by Wenckebach and Winterberg (p 511)

There is, moreover, a further relationship between emotion and extrasystoles, namely the arrhythmia causing anxiety and apprehension To most laypeople any irregularity of the heart's action spells "heart disease" and once the patient's attention is focused on the "missed beats" the increasing anxiety about his discovery is an important factor in increasing the number of extrasystoles (*see* also section on "Symptoms"). Thus in some instances it is difficult to decide whether anxiety or extrasystoles are the primary disturbance. If Stevenson *et al.* found anxiety patterns in eleven out of twelve unselected subjects with extrasystoles, doubts may be entertained whether such series consisted in fact of unselected individuals

The reverse phenomenon is also observed, namely the disappearance of extrasystoles due to emotion (Robinson and Draper) The commonest experience is the absence of extrasystoles on examination of patients whose history makes the presence of premature beats most probable and in whom they can be brought out by certain measures (exercise, amylnitrite) In such cases the emotional strain invariably associated with a medical examination, particularly by a "strange" doctor, temporarily abolished the arrhythmia (*see also* section

or the administration of epinephrine abolished ectopic arrhythmias Clinically the conclusion seems warranted that the causation by emotions of extrasystoles is dependent on a certain *milieu intérieur* the peculiarities of which are little known

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WENCKEBACH, K F,

Miscellaneous Clinical Conditions

Infectious Diseases

Since myocarditis is often a feature of the most diverse kinds of infections (coccal, virus, bacillary, protozoal) (Scherf and Boyd, Saphir) it is easily understood that extrasystoles occur frequently in their course With the exception of diphtheria, in which the primary cardiac lesion is degenerative, with reactive inflammatory changes, no systematic investigations are available about the rate of incidence and the various types of extrasystoles in individual infections and no useful purpose would be served by undertaking such studies. Brief references to some papers on this subject may, however, not be amiss

In view of the frequent involvement of the myocardium in *diphtheria* extrasystoles should be expected to occur frequently in this disease, but reports about their incidence vary considerably.

The great discrepancies become evident by comparing the papers of Seckel and of Shookhoff and Taran (1931b) whereas the former reported extrasystoles in thirty-four out of seventy-five cases of diphtheria (45 per cent)—only ten of these patients showing clinical evidence of myocardial involvement—the latter found only one instance of (auricular) extrasystoles in fifty patients In a series of ninety cases Marvin found only two instances of auricular and one of ventricular extrasystoles Such differences may, at least partly, be due to the method of examination, thus, a longer rest before examination, a prolonged period of observation, an investigation carried out by a physician who is familiar to the child, all this may result in a lower heart rate and thereby in the occurrence of more numerous extrasystoles

20 per cent of 242 cases

Disagreement also exists about the most frequent site of origin of extrasystoles in diphtheria: predominance of auricular extrasystoles was found by Gunson and by Koppang, of ventricular ones by Begg and by Smith We are in agreement with the latter view. Occcasionally multiform extrasystoles and even short bouts of paroxysmal tachycardia with alternating ventricular complexes were reported (Stecher).

Gunson's statement that the occurrence of extrasystoles in diphtheria was of no material prognostic significance and did not indicate the necessity of bed rest is not acceptable to us. Actually, Hume pointed out long ago that, in this condition, extrasystoles may occasionally be the first sign of myocardial involvement

In *lobar pneumonia* extrasystoles were described by de Graff, Travell and Yager. Mackenzie (1902) considered them to be an ominous sign, but modified this statement in his later writings Extrasystoles were described in *scarlet fever* by Kiss and Romhányi, but thought to be rare in this condition by Shookhoff and Taran (1931a). In *bacterial endocarditis* they were seen in 7 per cent. by Segal Chagas and Villela described a cardiac form of *trypanosomiasis* with many ventricular and also auricular extrasystoles; this was confirmed by Arrillaga, Soldati and Gandulla

Rheumatic fever

In this condition extrasystoles were described as a common occurrence (Peel); they were seen in 25 per cent. of the cases (Campbell) Their occurrence is considered to indicate active myocarditis

Scorpion's bite

An observation of tachycardia with extrasystoles caused by scorpion's bite has been reported by Celoria and Sloer

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EXTRASYSTOLES AND LIFE INSURANCE

In the assessment of proposals for Life Insurance the finding of extrasystoles is an important factor While with some companies their presence alone appears to preclude acceptance at the normal premium even in the absence of any other pathological finding (Salvesen), a more scientific and discriminating approach prevails with others and every case tends to be judged on its own merits

In order to obtain some information about the attitude taken by Insurance Companies towards applicants who have extrasystoles, but are otherwise healthy, we directed an inquiry about this to fifteen of the leading Life Insurance Companies of the United States and Great Britain. We received informative and often detailed replies for which we should like to express our appreciation to the companies concerned

Two points were emphasized in many of such replies: The fact that each application is considered individually, and the practice to accept applicants as "good average" (first class) lives if they are healthy in every other respect.

Individual companies vary regarding particular points to which they attach special importance These are summarized in Table 5, in which such factors are marked by + It is based on the more detailed replies which we received from eleven companies

TABLE 5

Company	Number of es per minute	Runs of es	Age of patient	Persistency of es	Rate of basic rhythm	Appearance or disappearance after exertion	Multiform es	Changes in T-waves of post-extrasystolic beat
1	+		–					
2	+	–			+	+	+	
3	+		+			+		
4	+					+		
5		+	+				+	+
6	+		+			+		
7				+				
8	+		+	+				
9	+					+		
10			+					
11	+		+		+			

es = extrasystoles

The table shows that most companies pay much attention to the number of extrasystoles per minute. According to one, more than eleven extrasystoles per minute indicates a substantial increase in risk. Another holds that the risk increases with age and with increase in the number of persistently intermittent pulses. This company instances an example that, at the age of fifty-six with an intermittent pulse of under five per minute, a mortality of 80 per cent. in excess of the normal should be expected; with five to ten per minute the expected mortality should be regarded as twice the normal. The same Company attached an extract from a book written by Dingman on the subject of " Risk Appraisal " in which the effect, on the mortality ratio, of pulse intermittence is detailed. This extract shows that such pulse intermittency comprised extrasystoles and dropped beats between which no distinction seems to have been made. An approach which does not distinguish between these basically different kinds of arrhythmias seems to us highly questionable.

In our opinion the number of extrasystoles alone cannot be held to be a valid criterion regarding life expectation. Since we consider true extrasystoles to be due to an abnormality in one circumscribed focus (*see* chapter on " Mechanism ") and such an ectopic centre to consist of a very small number of cells—perhaps only one cell—it will depend solely on the degree of the abnormality in such a small area whether one extrasystole will occur per minute, or many. Thus, even if one extrasystole follows each normal beat and bigeminal rhythm prevails, such an arrhythmia does not denote that the individual should be regarded as a more serious risk than those who have only three or five premature beats per minute

Even if short runs of extrasystoles occur, the importance of which was stressed by two companies, the heart often is normal in every other respect, as it actually is in the majority of individuals with supraventricular paroxysmal tachycardia. We agree, however, that in such instances the case should be treated individually and with special caution, as in the event of auricular extrasystoles there is an increased probability of auricular fibrillation occurring

Another point, to which great importance is attached by several companies, is the age at which extrasystoles occur, or are found. In our opinion this is fully justified, since in individuals over forty premature beats may be an early sign of coronary disease One company disregards extrasystoles in applicants under forty, but in those over forty an extra premium is asked for Other companies draw the line at forty-five beyond which they request a moderate increase in premium

A further point, stressed by two companies, is the persistency of the extrasystolic arrhythmias. Thus, one company accepts such applicants only at an additional premium. The evidence available about persistent premature beats does not appear conclusive for forming an opinion whether this attitude has a foundation in fact and it seems to us that, in such cases, individual assessment is of particular importance.

We would advocate the same attitude regarding extrasystoles occurring with sinus rhythm of higher rates. Here, the length of coupling is a decisive factor: extrasystoles with short coupling, that is occurring early in diastole, may and do occur in tachycardia, whereas those with longer coupling require a diastolic period of greater length to become manifest and therefore are seen only with slower rates. As there is no reason to attach a prognostic significance to the length of coupling it seems highly dubious in applicants with extrasystoles to expect a higher mortality in those with a faster S-A rhythm (Berliner and Huppert).

We concur with the view that extrasystoles occurring during or shortly after exercise,

The significance of alterations in the T wave of the first post-extrasystolic beat, which was mentioned in the reply of one company, is discussed on p. 37.

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INCIDENCE OF EXTRASYSTOLES

Introductory Remarks

There seems hardly a human being who at one time or another has not had extrasystoles. They may be, and often are, accidentally found during a medical examination, the subject being quite unaware of their presence The reverse is equally common: some symptoms entirely due to extrasystoles made the patient seek medical advice, but none are found on examination Some emotional tension inevitably caused by the investigation abolished all arrhythmia during the crucial half-hour or so of the examination, via changes in autonomic nervous tone; often some slight increase in rate occurs which shortens the diastolic phase. For these reasons statistics about the frequency of extrasystoles have a very limited value In order to be reliable regarding diagnosis, they should be based on graphic records, preferably electrocardiograms, otherwise they will be almost valueless for demonstrating the true incidence amongst the general population. Even regarding the frequency with which extrasystoles occur amongst patients, hospital or private, wide differences in the figures have to be expected because of the inevitable selection of cases for such an investigation Thus the incidence will vary according to whether such statistical studies are undertaken in a general hospital or in a cardiac department, in a more general private practice or in one with predominantly cardiac patients, whether, regarding age groups, a cross-section of the whole population is examined or the study is based on the older age groups in which coronary sclerosis forms a significant predisposing factor, rendered even more important by the exhibition of digitalis, particularly if this drug is given in larger doses. A cardiologist will see more cases with extrasystoles than a general physician

With these reservations a few statistical investigations may be quoted in order to convey some general impression about the frequency with which extrasystoles have been encountered in different circumstances

General Incidence

Amongst 5,124 males examined for life insurance extrasystoles were found in 194, that is 3 8 per cent. (Leslie) In a group of 500 recruits for the Royal Canadian Air Force the incidence of extrasystoles was twelve, that is 2 4 per cent (Stewart and Manning), and in one of 1,000 aviators of the American Air Force, fifteen (1 5 per cent) (Graybiel *et el*)

Passing from these sections of the general population to hospital patients generally and cardiac patients in particular, a higher incidence of extrasystoles tends to be encountered. Some relevant data are summarized in Table 6 The wide variations in these statistics are evident

Incidence of Extrasystoles in Subjects with Normal and Abnormal Cardiac Conditions

To what extent does the occurrence of extrasystoles indicate a pathological cardiac condition? Does the incidence of extrasystoles in normal subjects and in cardiac patients, as revealed in investigations on larger series, provide any reliable evidence about this problem? The answer, unfortunately, is in the negative. the figures in different investigations (*see* Table 7) vary to such an extent that nothing but a general impression is obtained

TABLE 6

INCIDENCE OF EXTRASYSTOLES AMONGST HOSPITAL PATIENTS GENERALLY AND CARDIAC PATIENTS

Number of Patients examined	Number of Extra-systoles	Per cent.	Remarks	Author
10,000	1,503	15	Patients electrocardiographed 1914–1931 at Massachusetts General Hospital	White, 1944
25,000	3,034	12	Patients electrocardiographed 1934–1943 at Massachusetts General Hospital	White, 1944
16,810	—	1	Patients electrocardiographed 1940–1942 at Metropolitan Hospital, New York. Electrocardiograms are taken routinely	Scherf
12,473	286	2·3	General Hospital, medical cases	Laake
6,000	270	4·5	—	Unghváry
2,500	—	*ca* 70	Patients examined for cardiac complaints Extrasystoles either deduced from history or present on examination	Holzmann
500	—	*ca* 20	Consecutive series referred to a Cardiographic Department	Campbell

TABLE 7

INCIDENCE IN PER CENT., AMONGST CASES WITH EXTRASYSTOLES, OF PATIENTS WITHOUT ANY EVIDENCE OF ANY OTHER CARDIAC ABNORMALITY.

Number of patients with extra-systoles	Incidence in per cent of patients without any evidence of any other cardiac abnormality	Remarks	Author
1,142	54	Examination for Life Insurance.	Ungerleider and Gubner
194	34·2	Examination for Life Insurance, 34·2 per cent with evidence of heart disease, 31·6 per cent. borderline cases	Leslie.
100	55	Consecutive cases in a naval hospital	White, 1927
278	55	—	Wenckebach and Winterberg
184	32·5	—	Peel.
231	46·8	Patients aged 75–96	Willius
216	7	Hospital patients 81·5 per cent had evidence of heart disease, 11·5 per cent were suspect of heart disease	Unghváry.

A reasonable estimate seems to be that in 30–50 per cent. of hospital patients with extrasystoles the cardio-vascular system is otherwise normal This proportion is much larger in patients seen in private practice. Contrariwise, the incidence of extrasystoles in patients with coronary sclerosis is considerably greater than in the general population and further enhanced if digitalis is given. This also accounts for the more frequent occurrence of extrasystoles in old age (*see* below) Similarly, certain infections predispose to premature beats,

Incidence of Different Types of Extrasystoles

Table 8 shows the distribution of extrasystoles according to their site of origin It will be seen that, on the whole, the figures of the several authors are in satisfactory agreement. Auricular extrasystoles are much less common than ventricular ones, the incidence of the former being, on an average, about half that of the latter

TABLE 8

DISTRIBUTION OF EXTRASYSTOLES ACCORDING TO THEIR SITE OF ORIGIN

Number of Tracgs exam'd	Number of Extrasystol	Per cent	Ventr	Per cent	Supra ventric	Ventr and Supra ventric	Remarks	Author
1,000	15	1·5	8	53	7	0	Young healthy aviators	Graybiel *et al*
500	12	2·4	9	77	3	0	Young healthy aviators	Stewart *et al.*
10,000	1,503	15·5	974	65	529	0	Patients in general hospital	White, 1944
25,000	3,304	12·1	2,007	66	1,027	0	Patients in general hospital	White, 1944
12,473	286	2·3	181	64	105		Patients in general hospital	Laake
6,000	216	3·6	98	45	57	61	Hospital patients	Unghváry
3,269	251	6·8	167	67	84		Only cases without organic heart disease	Nathan
?	194		120		61	6	Only cases with extrasystoles examined In 7 cases origin undetermined	Leslie
500	114	22·8	70	61	44		Patients of a Cardiographic Department	Campbell
5,600	86	1·5	52	60			Children under 16 attending cardiac clinic	Landtman
?	1,142		758	66	384	0	Only cases with extrasystoles examined	Ungerleider and Gubner
24,000	398	1·9	141	62	38	49	Only in 228 cases extrasystoles classified	Dauwe
941	160	17·0	74		60		Only patients over 51 In 26 cases origin of extrasystoles undetermined	Martinez
300	38	12·6	15	39	19	4	Ambulatory patients over 60 55·6 per cent were 70–79	Fox *et al*
100	20	20·0	15	75	5	0	Patients over 70	Eliaser and Kondo
315	108	34·2	57	53	51	0	Patients aged 75–96 without cardiac disease	Willius
385	123	31·9	83	68	40	0	Patients aged 75–96 with cardiac disease	Willius
700	231	33·0	140	60	91	0	Total of Willius' series	
100	31	31·0	10	32	21	0	Patients aged 80–103 Average age 84·2	Wosika *et al*

One or two common pitfalls in the classification of extrasystoles should briefly be mentioned. In many instances, the P waves of auricular extrasystoles are buried in the T waves of the preceding beat Unless such a record is carefully analysed, the auricular extrasystoles are apt to be misinterpreted, either as ventricular ones, if the ventricular complexes are abnormal owing to aberrant conduction in the ventricles, or as A-V nodal ones, if the ventricular complexes are of normal shape. We believe that the incidence of A-V nodal extrasystoles, as given in some statistics, is too high because of the inclusion, in this category, of

auricular extrasystoles with indistinct or invisible P waves. The employment of chest leads with the exploring electrode on the right sternal border, or of unipolar limb or oesophageal leads, may clarify this distinction. In our opinion A-V nodal extrasystoles are rare and in all cases, in which the differential diagnosis between auricular and A-V extrasystoles is in any doubt, the term "supraventricular extrasystoles" should be employed. This practice has been adopted in our Table 8.

Regarding the incidence of various types of extrasystoles in relation to the cardiac condition of the patient, it may be mentioned that in Ungerleider and Gubner's series ventricular premature beats occurred less frequently in cases with cardiovascular disease, the figures being 61 and 72 per cent. respectively In old people the reverse relationship was found by Willius (*see* Table 8)

Sex

It seems that extrasystoles occur with about equal frequency in the two sexes (Gallavardin, Campbell), though some authors report some slight predominance amongst males (Goodall, White 1926) The latter found in a series of 1,500 private patients that amongst 103 with extrasystoles and structural heart disease fifty-eight were men and forty-five women and a similar sex incidence was found regarding patients with extrasystoles and a normal cardiovascular system Some predominance of males would be understandable *in view of the greater incidence of coronary sclerosis in men, but this would be compensated,* at least partly, by the tendency of extrasystoles to occur during menstruation and pregnancy. Laake reported a preponderance of females in each age group

Age

Extrasystoles have been observed at all ages, including the foetal heart and at birth.

In a study on the incidence of foetal arrhythmias, Sontag and Newbery found that extrasystoles appeared about sixty days before birth, attained their maximum frequency about one month later, then became rarer and disappeared about one week before delivery Their appearance and disappearance was considered related to the stages of development of the autonomic nervous system. Hyman considered arrhythmias between the fifth and eighth lunar months as not uncommon, opinions about their incidence, which he endeavoured to ascertain by means of a questionnaire sent to 100 obstetricians, varied widely, *namely, from 0 to about 25–33 per cent of all cases examined prenatally* In a phonocardiographic study of foetal heart sounds Hyman encountered six instances in which extrasystoles were suspected on the grounds of the phonocardiogram, after birth the diagnosis was confirmed when right ventricular premature beats were found. In all cases the arrhythmia disappeared within a few days, as was also found by Holtermann.

Regarding new-born infants, Hecht reported a case in which blocked auricular extrasystoles were observed for seventeen days after birth, but the arrhythmia had already been noticed during delivery Auricular extrasystoles observed in such circumstances may be persistently or occasionally blocked (Antoine; Rihl and Weinzierl, Fenichel and Kurzrock) or conducted (Barre and Henriet) On clinical examination Lyon and Rauh found extrasystoles in three amongst 5,114 newly born infants (0 06 per cent)

(Burghard and Wunnerlich claimed to have recorded interpolated extrasystoles in ten out of thirty-two normal new-born infants, and Raiha to have found ten instances amongst forty-five premature babies examined two to twenty-four hours after birth, but the reproduced tracings of these authors show only artefacts)

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It

Some figures about the incidence of premature beats in children are given in Table 9. Several of the authors quoted in this table mention that they have no prognostic significance and they cannot be taken to indicate an abnormal heart (also Leffkowitz) According to Gelman and Brown they increase in frequency at puberty Whether extrasystoles occur more frequently in children with cardiac disease seems uncertain, while the figures obtained by Lyon and Rauh in their various series seem to indicate this, the figures of the various investigations tabled differ to such an extent that no definite conclusions can be drawn in this respect.

TABLE 9

INCIDENCE OF EXTRASYSTOLES IN CHILDREN

Type of Group	Number exam'd	Number with Extra-systoles	Per cent	Remarks	Author
Normal children	2,672		2.2		Lyon and Rauh
	259	2	0.8		Shookhoff and Taran
	100	1	1		Perry
	100	2	2		Hafkesbring *et al*
Schoolchildren	1,782	40	2.2	Ages under 10 to 19	Lyon and Rauh
Children amongst patients of all ages with extrasystoles	226	7	3.1	Ages 10 to 19	Cowan and Ritchie
	100	3	3	up to 14	Smith
Hospital patients generally	1,000	48	4.8	Diagnosis made only by clinical impression	Visco
	400	0	0		Antell
Children attending cardiac clinic	5,600	86	1.53	Children under 16 In most cases predisposing factor present e g infection Good prognosis Includes 200 normal controls	Landtman
	782	35	4.4	Ages 2½–14½	Lyon and Rauh
Children with cardiac disease	100	1	1	Rheumatic heart disease	Drawe *et al*
	100	0	0	Congenital heart disease	Drawe *et al*
	468		4.3		Lyon and Rauh

Regarding middle-aged and elderly subjects, there can be no doubt that extrasystoles are a very common occurrence (*see* Table 10) Their frequency tends to increase with age, as also observed by Laake Generally, ventricular origin of the premature beats is commoner than auricular one (*see also* Table 8) The high incidence of extrasystoles in the [illegible]

Heredity

Little is known about heredity of extrasystoles An octogenarian "cardiac" reported in a letter to the *British Medical Journal* that he had had extrasystoles since the age of fourteen and that his father and two sisters had the same condition.

TABLE 10

INCIDENCE OF EXTRASYSTOLES IN MIDDLE AND OLD AGE.

Age Group	Number examined	Number with Extra-systoles	Per cent	Remarks	Author
Over 51	941	160	17	52 per cent. aged 51–60	Martinez
Over 60	300	38	12 6	Ambulatory patients	Fox *et al*
60–90	102	9	8 8	Non-cardiac patients	Taran and Kaye
Over 70	100	20	20	" " "	Eliaser and Kondo
Over 70	100	23	23	" " "	Levitt
Over 70	100	28	28	" " "	McNamara
75–96	700	231	33	108 without, 123 with cardiac disease. *See also* Table 8	Willius
80–103	100	31	31	Consecutive cases Average age 84 2	Wosika *et al*

SUMMARY

Reasons are given for the view that all statistical studies about the incidence of extrasystoles in the general population have only a very limited value. With this reservation some relevant papers are discussed which deal with the incidence of extrasystoles according to the presence or otherwise of cardiac disease, site of origin of the premature beats, sex, and age According to a very approximate estimate, in 30–50 per cent of hospital patients with extrasystoles the cardio-vascular system is otherwise normal and this proportion is much higher in patients seen in private practice The incidence of auricular extrasystoles is, on an average, about half that of ventricular ones. Premature beats seem to occur with about equal frequency in the two sexes. The presence of extrasystoles in the foetus and at birth can be considered as established In middle-aged and elderly subjects extrasystoles are a very common occurrence and their incidence tends to increase with age Even in very old subjects their presence need not have any more serious significance than in younger persons In view of the wide variations of the figures in the various series no more definite conclusions about their rate of incidence in the various circumstances can be drawn

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DURATION

Most individuals exhibiting extrasystoles have them only occasionally. The premature beats occur singly and sporadically, being separated by long periods of normal sinus rhythm. There are many who have extrasystoles for only a few minutes or hours and are entirely free from them for many months or years. We know of persons in whom they occur only in spring but not during the rest of the year.

Extrasystoles may persist for many years in otherwise healthy individuals It is by no means uncommon to be told by a patient that he has had the irregularity "ever since I can remember". Cases are on record in which extrasystoles were observed for twenty-four (de Graff and Batterman), forty-six (Esler and White), fifty (Mackenzie) and sixty-seven years (Grassmann) Walsh observed ventricular extrasystoles on himself for forty years.

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SYMPTOMS

In a great majority of cases extrasystoles do not give rise to any symptoms. Even in individuals who have premature beats for a lifetime they may be asymptomatic. On the other hand, extrasystoles often cause symptoms of greater or lesser severity, ranging from an occasional slight momentary discomfort to one of such agony that it becomes frankly disabling

Not infrequently symptoms date from the moment a doctor told the patient that his heart action was irregular, or from the patient's accidental discovery of the arrhythmia. Once the patient's attention is focused on his heart a vicious circle often starts, the patient's observing his heart action more closely resulting in more numerous extrasystoles and vice versa

There is hardly any other cardiac condition of which the patients' descriptions vary so much as extrasystoles The word most commonly used is palpitation. This term, employed by patients to describe many diverse conditions, refers, in the event of extrasystoles, not to any sustained or prolonged discomfort, but rather to repeated abnormal sensations, each of which is isolated and of short duration. Further questioning elicits a surprising variety of descriptive terms in different patients. Standstill of the heart, the heart [illegible]

more distinctly, content themselves with reporting a "funny feeling" (Fahr). Sometimes the description is coloured by analogies to other experiences the patient has had The woman who had borne children might compare the sensation caused by the extrasystole with that of quickening during pregnancy, the hunter with that of the quick turn of the hare, the athlete with a sudden jump

Sometimes extrasystoles give rise to m[illegible] of sudden tension, or one like the blow of [illegible] of oppression in the chest (Wenckebach [illegible] fullness in the throat (Leconte) Some French terms for such discomfort are: éclair douloureux, baillement avorté, and eructation imminente.

Occasionally extrasystoles give rise to frank pain (Gallavardin 1929, Wenckebach and Winterberg) This is of very short duration, but may be very severe (Wenckebach, 1903, 1914) In one of our patients it was so intense that it made him jerk his head off the pillow with every extrasystole, he compared the sensation with that caused by an electric shock.

More general sensations produced by extrasystoles include an indescribable anxiety, a sinking sensation, a peculiar feeling of emptiness, one of being conscious of the heart beat, and dizziness. The last may be associated with vertigo and pallor, particularly if longer series of such ectopic beats occur Cerebral anaemia was considered the underlying mechanism by Wenckebach (1898) Regarding this last group of symptoms, it is often impossible to be certain whether they are due to the arrhythmia, or to an underlying anxiety state or neurocirculatory asthenia which are themselves so often responsible for, or co-exist with, extrasystoles (*see also* p 448).

Gallavardin (1914) reported an observation in a sixty-three-year-old man with syphilitic aortic incompetence in whom auricular extrasystoles, occurring periodically and then nearly always in the form of auricular bigeminy, precipitated vertigo and syncope closely resembling Stokes-Adams attacks.

Opinions about how extrasystoles give rise to the various symptoms vary and much is still controversial. The common varieties of palpitations, described above, are attributed to the same mechanism which is responsible for the accentuation of the first sound of the extrasystole (Ungerleider and Gubner) (*see* pp 463 *seq*) Others, for instance Wenckebach and Winterberg, hold the view that such sensations are produced by the first post-extrasystolic beat because of its larger stroke volume The observation that patients suffering from a concomitant cardiac condition resulting in an increased stroke volume (for example, aortic incompetence) experience particularly unpleasant sensations from extrasystoles tends to support this view. This conception does not, however, explain certain other symptoms commonly associated with this arrhythmia. In cases with single isolated extrasystoles, for example, dizziness associated with a feeling of standstill of the heart might be attributed to the long post-extrasystolic interval. It is true that in patients with advanced arteriosclerosis the diastolic blood pressure may fall to very low levels during a long post-extrasystolic interval and dizziness be produced in this way If it is remembered, however, that much longer intervals between successive ventricular beats, as they occur in various kinds of heart block and in other conditions, do not produce any symptom of this kind, it becomes obvious that this cannot be the general explanation It seems probable that the extrasystole itself causes the sensation which is interpreted as standstill and gives rise to the feeling of unsteadiness This view is supported by Kline and Bidder's recent investigation on the origin of symptoms produced by extrasystoles, which showed that they are caused by the premature contractions themselves Moreover, in some patients with auricular fibrillation and extrasystoles, only the latter produce unpleasant sensations which disappear if the ventricular ectopic beats are abolished while auricular fibrillation continues

An unusual symptom of some physiological interest is a short cough accompanying each extrasystole (Leconte) We encountered this phenomenon about ten times and in one further case a short cough invariably heralded the onset of an attack of auricular fibrillation lasting on an average six hours This kind of cough occurs without any warning and to the patient is both ominous and embarrassing as he realizes the invariable association with the cardiac arrhythmia and is taken by surprise by it It appears to be due to a reflex within the autonomous nervous system, with the receptors in the heart itself

Discussion of symptoms may be concluded by a reference to notes left by a medical student, apparently a non-neurotic subject, giving a vivid description of the suffering which [illegible]

Each [illegible] within the narrow and limited [illegible] ncompetence, the aggravating [illegible] was already referred to. But even with a combination of these conditions, suffering of such intensity fortunately is quite exceptional.

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SIGNS ON PHYSICAL EXAMINATION

Inspection and Palpation

These two methods can with advantage be considered together. Both were used a long time before the modern graphic registration of arrhythmias had become possible.

Inspection refers to the jugular veins and to the praecordial area, particularly the apex beat, palpation to the latter and to the radial and carotid pulse.

In an otherwise uncomplicated case with occasional single extrasystoles the individual premature beat gives rise, in the jugular veins, either to several smaller pulsations or to one larger wave, depending on the time of occurrence of the extrasystole.

If a premature beat falls at such a time that an auricular and a ventricular contraction occur simultaneously, or nearly so, the flow of blood in the normal direction from auricles to ventricles is temporarily obstructed and a large amount of blood ejected backwards into the jugular veins, there giving rise to a much larger pulsation than those due to the normal beats Such conditions obtain if a premature ventricular systole occurs at about the time of the next auricular contraction, or if an auricular extrasystole coincides with the preceding ventricular contraction—this is common in auricular extrasystoles—or in the case of atrio-ventricular extrasystoles Failing such time relations between auricular and ventricular contraction the premature beat gives rise to two or three smaller pulsations, the nature of each of which, though analysable in graphic records, cannot be determined by inspection

On inspection and palpation of the praecordial area the extrasystole produces a premature apex beat which often differs in character from that of the normal ones, being sometimes weaker, but more often more forceful and abrupt; it is followed by a longer pause.

In the radial and carotid pulse the extrasystole gives rise, either to a premature smaller pulse, its volume and timing depending on the degree of prematurity of the extra-contraction, which is followed by a longer pause, or to no palpable pulse. Many examples are contained in Mackenzie's book on the pulse (1902) In some instances a smaller pulse may be palpable at the carotid, but not at the radial arteries, in others a pulse is absent in both

The absence of a palpable arterial pulse may be due, either to the failure of the extra-contraction to eject a sufficient amount of blood with a pressure adequate to open the aortic valves—this occurs most commonly in the case of very early extrasystoles—or to failure of the extrasystolic impulse to activate the ventricles which characterizes blocked auricular and certain rare varieties of atrio-ventricular extrasystoles.

If extrasystoles occur more frequently, and particularly if one premature contraction follows each beat of the dominant rhythm, the resulting bigeminal action has given rise to

controversy and great confusion in the past (*see* chapters on "Alternans" and on "Coupling") If, with bigeminal action, the extrasystoles fail to produce a palpable pulse at the wrist, the pulse rate is half the ventricular rate, the resulting rhythm being one variety of "pseudo-bradycardia". The first report of such an observation of what was then thought a "double contraction" of the heart in relation to the pulse seems to be contained in a paper by Charcelay published in 1838 The slow pulse is only too readily interpreted as indicating "bradycardia" and such misinterpretation is not infrequently carried a step further, particularly in over-digitalized patients with bigeminal action, by diagnosing "heart block". In such instances inspection of the jugular pulse might well suggest the correct diagnosis which can then be substantiated by auscultation and, if necessary, established beyond doubt electrocardiographically (*see also* section on "Diagnosis")

In interpolated extrasystoles the extracontraction gives rise to jugular pulsations and to an apex beat which are interspersed between two consecutive ones following one another in the regular sequence of the dominant rhythm, no longer pause follows the last of such a group of three beats. The arterial pulse changes are described in the section on interpolated extrasystoles. Without auscultation, neither palpation of the arterial pulse nor inspection of the jugular veins will make the diagnosis possible which often necessitates the employment of graphic methods

Auscultation

Just as apex beat and arterial and venous pulses, so were the heart sounds, produced by premature contractions, studied long before the mechanism underlying the several varieties of intermittent pulse could be analysed according to modern standards The discrepancy between a stronger and more forceful apex beat, an accentuated, loud, booming first sound, and a weak pulse—which combination characterizes a large proportion of premature beats [illegible]

Quincke and already at that time attributed by him to lack of normal co-ordination in the mode of contraction of such beats, the effect of contraction of different parts of the heart partially cancelling one another, perhaps under the influence of abnormal innervation

These conditions were studied especially in connexion with premature beats which did not give rise to a palpable pulse at the wrist or over the carotids Early investigators were Bozzolo (1876), one of the earliest correctly to attribute the small or absent pulse to inadequate filling of the ventricles and rejecting the then accepted theory of hemisystole (*see* chapter on "Historical Remarks") [illegible] and clinical observation, gave tl [illegible] Hochhaus and Quincke (1894) w [illegible] Hochhaus (1907) who stressed that the prematurity of such contractions is not the sole essential feature, but that the qualitative difference as manifested in the different character of the apex beat and of the sounds were of fundamental importance Korányi's paper may be quoted parenthetically as indicating that, as late as 1908, a confusion could exist between time relations and relations of strength of such beats, and that conclusions about their diagnostic significance, functional effect and underlying mechanism could be put forward which nowadays can only be termed fantastic

The majority of extrasystoles produce two sounds, but if the premature contraction fails to open the semilunar valves, only the first sound is present In the case of bigeminal rhythm this may easily be confused with gallop rhythm

That the first sound of extrasystoles often is accentuated and of a quality different from that of the normal beats was noticed by many observers, for example, Quincke, Hochhaus

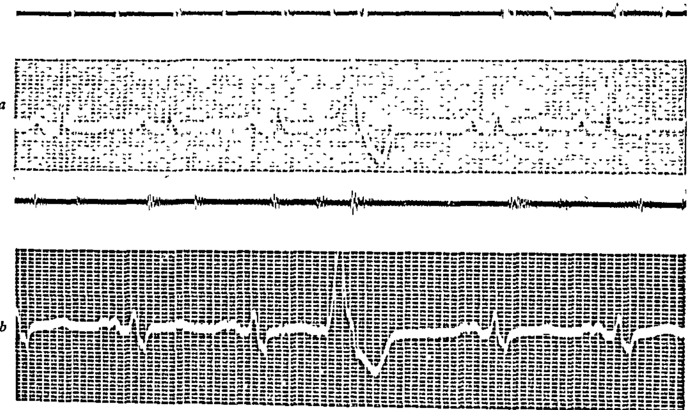


FIG. 201—*a* and *b*
For explanation, see legend to Fig 201.—*c* on next page

and Quincke, Hochhaus who stressed its booming character, Wenckebach (1898, 1903) who called it "dumpf" (dull). At first this accentuation was explained by the qualitative difference in the mechanism of the extracontraction (Gerhardt, Hochhaus, 1907) and of the ejection of the blood (Leconte). It was also stated that the first sound of an extrasystole is particularly accentuated over that ventricle which is primarily under strain to maintain compensation (Korányi, Leconte) In other instances both sounds may be faint or even absent, as was noted by Mackenzie.

Some of these conditions are illustrated in the phonocardiograms reproduced in Fig 201.

Phonographic investigations have shown that the first sound of extrasystoles may be louder or fainter than that of the normal beats and that the underlying mechanism is closely related to that responsible for the intensity of the first sound generally It is now accepted that this depends, above all, on the position of the A-V valves at the beginning of ventricular contraction This view was first put forward as

portance of the degree of tension of the valves at

affirmed, within limits, by the original authors (1950). The position of the A-V valves changes during auricular systole (Dean) and, whatever the finer mechanism of this may be, it is fairly certain " that the eventual position of the valves at the moment of ventricular systole is the determining factor in the intensity of the sound produced " (Levine and Harvey, p 17) The A-V valves are at first propelled downward into the ventricular cavities with auricular systole and then gradually proceed to a higher level Therefore, if the ventricles contract very soon after the auricles (P-R· 0·04–0·12 second), the leaflets " are quite low and relaxed and snap back a considerable extent This results in a loud sound " If the ventricles contract at a time longer than normal after the auricles (P-R 0·22–0 30 second), the valvular leaflets have already ascended to a higher position in the ventricles " with the

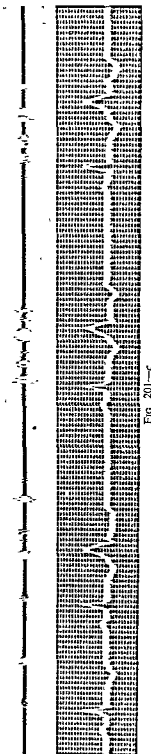


Fig 201—c

Fig 201 —Phonocardiograms of three instances of ventricular extrasystoles *a* and *b* on preceding page show that the extrasystole had produced only one sound Fig 201—*c* shows two sounds produced by each extrasystole In all instances the first sound of the extrasystole was louder than that of the normal beats This is particularly pronounced in Fig 201—*c*, which demonstrates, in addition, a systolic murmur in the first post-extrasystolic beats which was not recorded with the other sinus beats

slack taken up " and the first sound produced by the ventricular contraction in such circumstances is fainter (Levine and Harvey)

It was pointed out by Wolferth and Margolies (1930b) that, both in auricular and ventricular extrasystoles, the intensity of their first sound is dominated by the time relation between the beginning of the P wave and the first sound of the premature beat, rather than by the degree of prematurity of the extrasystole. This could be established by comparing the intensity of the first sound of extrasystoles with that of beats with a similar degree of prematurity in auricular fibrillation With the exception of " very highly premature " beats the first sound of extrasystoles tended to be louder than that of the normal ones if the interval· beginning of P—first sound was less than that of the normal beats.

Cossio, Dambrosi and Warnford-Thomson investigated the first sound in auricular and ventricular extrasystoles in some finer detail. In all but one of sixteen cases with *auricular* extrasystoles the extrasystolic first sound was louder than that of the preceding and succeeding normal beats and, compared with the normal beats, the accentuated first extrasystolic sound occurred with a delay of an average of 0 03 second in relation to the QRS complex of the extrasystoles. Both the increased intensity and the delay of the first sound of the extrasystoles were most pronounced if the premature beat occurred in mid-diastole of the preceding beat Amongst fourteen cases with *ventricular* extrasystoles the extrasystolic first sound was louder than the normal first sound in nine, of equal intensity in one, of equal or less intensity in one and of less intensity in three cases; in all instances it was delayed, in relation to the onset of the QRS complex, by an average of 0 05 second. It was of greater intensity if the premature contraction occurred in mid-diastole of the preceding beat or just after the next normal P wave. The accentuation and delay of the first sound was more constant and more pronounced in auricular than in ventricular extrasystoles This was attributed by these authors to several factors: auricular extrasystoles generally occur at a moment propitious for the accentuation of the first sound; ventricular filling is more complete in auricular than in ventricular premature beats; lastly, in the former variety the normal synchronism in the closure of the tricuspid and mitral valves which, by way of summation contributes much to the production of the first sound, is undisturbed whereas, in ventricular extrasystoles, there is asynchronism in the contraction of the two ventricles The latter factor also accounts for the authors' observation that in four of the fourteen cases of ventricular extrasystoles their first sound was split whereas that of the normal beats was not, such splitting of the first extrasystolic sound was never observed in the case of auricular premature beats. This accords well with the findings of Wolferth and Margolies (1935) that, in cases of bundle-branch block, the split first sound has a right- and a left-ventricular component and that separation of these components is due to asynchronism *in certain of the early phases of cardiac contraction in the two ventricles*

It was stated above that, in abortive extrasystoles, only one sound is produced by the premature beat While this is nearly always the first sound, Levine and Harvey published an instance in which only the second sound of a (ventricular) extrasystole was recorded (their Fig 105 on p 106) In the case of blocked auricular extrasystoles no sound may be heard or recorded

In nodal escape, in which the normally synchronized contraction of the two ventricles follows the preceding auricular one at a short interval, marked accentuation of the first sound may be noted (Levine and Harvey, Fig. 95 on p 98).

With interpolated extrasystoles the sounds of three beats occurring in quick succession are heard, such group being followed by a normal interval

In patients with systolic murmurs and extrasystoles the murmur usually is fainter in the extrasystolic beat. This was noted as early as 1884 by Stern (Case 2), also by Dehio (1891) and Hochhaus (1907) Weyler pointed out that diastolic murmurs cannot become manifest if the diastole is interrupted by an extrasystole; in such instances the murmur occurs in

the diastolic phase of the extrasystole, that is so late after the preceding beat that, unless this sequence of events is borne in mind, all sounds are erroneously attributed to the ectopic beat Systolic murmurs tend to be louder in the first post-extrasystolic beat.

The study of Wolferth and Margolies (1933) on gallop rhythm and the physiological third heart sound illustrates the value of " the method of extrasystoles " in the analysis of such acoustic phenomena These authors found that in all cases gallop as well as physiological third heart sounds fell without exception within one or both of two distinct time zones, namely: (1) 0·10–0 21 second after the beginning of the second heart sound, that is protodiastolic, or (2) 0 08–0·14 second after the beginning of the P wave, that is, presystolic. When these two time zones become superimposed, which may be due to a variety of causes (for example, tachycardia), gallop rhythm may either appear for the first time, or, if already present, become markedly accentuated, this is due to a summation phenomenon The effect of extrasystoles on gallop rhythm was instructive In three cases with rapid heart rates, loud gallop sounds and ventricular extrasystoles, the loud gallop failed to appear during the compensatory post-extrasystolic pauses, but in each case, during such pauses, either protodiastolic or presystolic gallop sounds or both were present When the regular tachycardia was resumed the loud gallop sounds immediately recurred This separation of a loud summation gallop into less loud protodiastolic, or presystolic sounds, or both, was attributed to the fact that the auricular contraction had become separated in time from the protodiastolic zone and thereby summation temporarily abolished Observations on two cases of auricular extrasystoles showed that, when the premature beats occurred at a time so that they were superimposed on the protodiastolic period of the preceding beat, a loud gallop sound invariably was recorded. This demonstrates that even an aberrant auricular contraction, timed in this way, is capable of producing a summation phenomenon One similar observation was made in respect of the physiological third heart sound in a young varsity oarsman with auricular extrasystoles the third sound was heard and recorded only when the auricular systole of the premature beats fell in the range of ventricular protodiastole, irrespective of whether or not the extrasystole was blocked Such observations were thus valuable for establishing that the gallop rhythm was, in fact, due to a summation phenomenon

SUMMARY

Inspection and Palpation

The apex beat produced by a single extrasystole is not only premature and followed by a longer pause, but also often differs in character from that of the normal beats

In the radial and carotid pulse an extrasystole either gives rise to a premature smaller pulse followed by a longer pause, or fails to produce a palpable pulse. The mechanism underlying the latter phenomenon is briefly discussed In the event of bigeminal heart action, due to one extrasystole following each beat of the dominant rhythm, absence of an extrasystolic palpable pulse results in the pulse rate being half the ventricular rate, in such cases the pulse often is slow and this may be misinterpreted as being due to bradycardia or complete heart block

Auscultation

The majority of extrasystoles produce two heart sounds, but if the premature contraction fails to open the semilunar valves only the first sound is present. If this occurs in association with bigeminal heart action such sequence of three sounds may be misinterpreted as gallop rhythm

slack taken up " and the first sound produced by the ventricular contraction in such circumstances is fainter (Levine and Harvey).

It was pointed out by Wolferth and Margolies (1930b) that, both in auricular and ventricular extrasystoles, the intensity of their first sound is dominated by the time relation between the beginning of the P wave and the first sound of the premature beat, rather than by the degree of prematurity of the extrasystole. This could be established by comparing the intensity of the first sound of extrasystoles with that of beats with a similar degree of prematurity in auricular fibrillation. With the exception of " very highly premature " beats the first sound of extrasystoles tended to be louder than that of the normal ones if the interval: beginning of P—first sound was less than that of the normal beats.

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CLINICAL DIFFERENTIAL DIAGNOSIS

Single Extrasystoles

On routine clinical examination an extrasystole is characterized by the signs of a premature contraction which is followed by a longer interval The presence of such a premature beat can without difficulty be ascertained by inspection, palpation, and particularly by *auscultation*, so *that the diagnosis* can easily be made *And extrasystoles are so much the* commonest cause of this kind of disturbance of rhythm that in the great majority of instances the clinical diagnosis will be correct

But this is not always the case In various chapters of this book conditions are described which can easily be mistaken for extrasystoles whereas their nature and clinical significance actually are entirely different Conversely, extrasystoles may be missed, or the extrasystolic arrhythmia erroneously be attributed to some other mechanism.

A few examples: dissociation with interference invariably conveys the clinical impression of an arrhythmia due to extrasystoles, in this instance the differential diagnosis can only be made by graphic methods The same holds good for that between extrasystoles in the strict sense of the term, as employed in this book, and parasystole, though in the latter the varying coupling may arouse the suspicion of a more complicated arrhythmia. Dropped beats after a varying number of conducted ones can, *to a certain extent, be distinguished* from extrasystoles by the absence of any sound indicating a premature beat, but without graphic methods a differential diagnosis between occasional dropped beats and blocked auricular extrasystoles cannot be made with any degree of certainty; only the differences in the [illegible] Occasional extrasystoles during

beats the differentiation from auricular fibrillation may be extremely difficult. Moderate exercise, for example, raising the body from the supine position a few times, or inhalation of amyl nitrite tend to increase the irregularity of rhythm in auricular fibrillation, whereas extrasystoles are likely to be suppressed by such measures and the rhythm thus tends temporarily to become regular, in this way a differential diagnosis is sometimes possible.

Attempts have repeatedly been made—in our opinion, without success—at distinguishing, by clinical examination alone, between auricular and ventricular extrasystoles. The only condition, in which we believe this to be possible, is mitral stenosis, if a distinct presystolic murmur not associated with a diastolic one is present over the apical region. If such murmur, which is due to auricular contraction, can distinctly be heard to precede the first sound of the extrasystole, its auricular origin can be assumed. In the presence of a diastolic murmur this method is unreliable since a diastolic murmur occurring immediately before an extrasystole may simulate a presystolic one (Mond) Mond claimed that the differ*entiation between auricular and ventricular extrasystoles was possible by ascertaining* whether the first alteration, produced in the venous pulse by the extrasystole, occurred before or after the first sound, the former indicating an auricular, the latter a ventricular origin of the premature beat We are not convinced that this method is either practicable—in many cases the several pulsations of the venous pulse cannot be distinctly seen—or reliable.

It has also been claimed that the distinction between these two types of extrasystoles could be made by tapping out the timing of the underlying rhythm, since this was shifted by an auricular, but not by a ventricular premature beat. This method is bound to be quite unreliable, in view of the great number of unpredictable factors which determine the length of the post-extrasystolic interval after an auricular extrasystole (*see* section on " Auricular Extrasystoles ") A simple sinus arrhythmia, too, makes such an attempt fail (Katz)

The first sound of extrasystoles may be louder or fainter than that of the normal beats of the individual case. The importance of the position of the A-V valves at the beginning of ventricular systole in determining the intensity of the first heart sound is emphasized. This, in the case of premature beats, is thus intimately related to the interval: beginning of the auricular contraction—first sound of the extrasystole.

In blocked auricular extrasystoles no sound may be present.

In nodal escape the first sound tends to be particularly loud.

In auricular as well as ventricular premature beats the first extrasystolic sound is delayed in relation to the QRS complex of the extrasystole, as compared with the time relations in normal beats In ventricular, but not in auricular premature beats the first sound is occasionally split, the underlying mechanism of this phenomenon is discussed

In patients with a systolic murmur and extrasystoles the murmur tends to be fainter in the premature beats. Diastolic murmurs may be delayed by an extrasystole, becoming audible in the diastolic period of the extrasystole

Observations on patients with gallop rhythm and extrasystoles supported the view that one form of gallop rhythm is a summation phenomenon, due to superimposition of acoustic phenomena occurring in two distinct portions of the cardiac cycle, namely a protodiastolic and a presystolic time zone.

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[illegible] ectopic beats Phono- [illegible]

which governs, in the first place, the physician's attitude and action. To the lay person irregular heart action spells heart disease and nowadays more people than ever are " heart conscious ". Nearly every one has had relatives or friends die of heart disease, often suddenly, and much publicity is given to this topic in the press and popular books, with the inevitable result that any irregularity in the customary rhythm of his pulse or heart beat makes the patient apprehensive of the dreaded disease

In the treatment of this group of patients the two most important conditions for success are: to take the patient's complaint seriously and to carry out a complete and thorough examination including the taking of a detailed history

The patient's complaints must be taken seriously if only because his physical symptoms, and even more his anxiety, are very real. To tell a patient, after a cursory examination, " your heart is perfectly sound and those few missed beats don't mean a thing " results only in the patient's seeking medical advice elsewhere, there are not many conditions in which patients change doctors as often as with extrasystoles.

A complete and thorough examination is indispensable, not only in order to exclude the presence of any other pathological condition, cardiac or otherwise, which may, and often does require treatment, but also for psychological reasons If a patient is to be reassured that he is otherwise healthy, which in this group of patients is the crucial and decisive therapeutic measure, such assurance must be given in an authoritative, decisive manner, making impossible any doubt in the patient's mind about its accuracy and good faith, and it can carry such weight only if the patient is convinced that all possible steps were taken to exclude any other disease

In taking a detailed history special attention should be paid to the patient's mode of life and habits. In quite a number of cases extrasystoles can be abolished if the patient gives up excess of coffee or tea, particularly if these beverages are taken strong, or if he reduces smoking, or changes his dietetic habits Regarding the last, the avoidance of flatulence, of indigestible articles of food or copious meals are points of special importance In others adequate treatment of constipation may cure the extrasystoles An enquiry into the taking of drugs should not be omitted: extrasystoles may be the result of the taking of thyroid for slimming, or of ephedrine or epinephrine (for example, for asthma) Regarding digitalis, *see* below under (3)

In some cases one has to go into great detail regarding the patient's habits Thus an elderly patient, who has been well known to one of us for many years, used to have numerous ventricular extrasystoles as a young man, without any evidence of any other cardiac abnormality The extrasystoles disappeared under appropriate treatment and were in abeyance for many years, until one day he again sought advice in great anxiety because " all my old trouble has come back " He was greatly troubled by numerous extrasystoles most of the early afternoon and closer questioning elicited the statement that, at the time the trouble recurred, he had adopted the habit of taking a cup of tea at about 3 p m Discontinuing this newly-acquired habit resulted in the prompt disappearance of the symptoms and it was noteworthy that, in his case, tea precipitated extrasystoles only when taken in the early afternoon whereas he could take a much greater quantity for breakfast without any ill effects.

Extrasystoles occurring during the menopause can often be successfully treated by means of ovarian hormone preparations if other measures, including sedatives, have failed In patients in whom premature beats appear during pregnancy assurance about their freque occurrence and their innocuous character is nearly always all that is required

In the majority of cases of this group, however, no such precipitating factor can

infrequently the first, or the presenting sign in patients with coronary sclerosis; in

shape of P waves.

As far as the small number of reported cases makes possible to judge the p significance, parasystole and return extrasystoles seem to occur predominantly in with structural heart disease. Dissociation with interference appears, on the wh to be associated with other cardiac abnormalities, toxic or structural in nature.

In practice, and considering extrasystoles and ectopic arrhythmias generally, hardly do better than apply to all age groups the precept which Ritchie gave in r patients over forty with extrasystoles, namely, to regard the presence of any ectopic mia with suspicion in every case and to examine the patient with every care. At tin examination will reveal—perhaps a hitherto unsuspected—cardiac disease, or son systemic disorder, for example, chronic gall bladder disease, and the prognosis will determined by that of the underlying condition, but in the great majority of insta extrasystoles will be found to be of the harmless variety and to have no prognostic cance.

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TREATMENT

βελτιστον δέ ἐστι αἰεὶ τὸ
προσωτάτω τοῦ ἀνεπιτηδείου ἀπεχον.

"The best advice is that which is least unsuitable."
Hippokrates *Tradition in Medicine.*
Trans by Chadwick and Mann

The great majority of patients with extrasystoles do not require treatment. The pa is not aware of the arrhythmia which in very many cases is harmless and often discov accidentally during a medical examination.

There are three main conditions in which extrasystoles necessitate treatment:

1. If in the absence of any other pathological condition they give rise to symptoms clinical importance, physical or psychological;

2. If they are very numerous;

3. If they occur in association with other pathological conditions in which they may initiate auricular or ventricular fibrillation, or may further impair cardiac function

1. Treatment of extrasystoles because of clinical symptoms, in the absence of any other pathological condition

While the great variety of symptoms which can be produced by extrasystoles is discussed in the appropriate section, it is the psychological effect of the irregular heart action which usually is the predominant cause to make the patient seek medical advice and it is this aspect

which governs, in the first place, the physician's attitude and action To the lay person irregular heart action spells heart disease and nowadays more people than ever are " heart conscious ". Nearly every one has had relatives or friends die of heart disease, often suddenly, and much publicity is given to this topic in the press and popular books, with the inevitable result that any irregularity in the customary rhythm of his pulse or heart beat makes the patient apprehensive of the dreaded disease

In the treatment of this group of patients the two most important conditions for success are. to take the patient's complaint seriously and to carry out a complete and thorough examination including the taking of a detailed history

The patient's complaints must be taken seriously if only because his physical symptoms, and even more his anxiety, are very real. To tell a patient, after a cursory examination, " your heart is perfectly sound and those few missed beats don't mean a thing " results only in the patient's seeking medical advice elsewhere; there are not many conditions in

that he is otherwise healthy, which in this group of patients is the crucial and decisive therapeutic measure, such assurance must be given in an authoritative, decisive manner, making impossible any doubt in the patient's mind about its accuracy and good faith, and it can carry such weight only if the patient is convinced that all possible steps were taken to exclude any other disease

In taking a detailed history special attention should be paid to the patient's mode of life and habits. In quite a number of cases extrasystoles can be abolished if the patient gives up excess of coffee or tea, particularly if these beverages are taken strong, or if he reduces smoking, or changes his dietetic habits Regarding the last, the avoidance of flatulence, of indigestible articles of food or copious meals are points of special importance In others adequate treatment of constipation may cure the extrasystoles. An enquiry into the taking of drugs should not be omitted extrasystoles may be the result of the taking of thyroid for slimming, or of ephedrine or epinephrine (for example, for asthma) Regarding digitalis, *see* below under (3)

early afternoon and closer questioning elicited the statement that, at the time the trouble recurred, he had adopted the habit of taking a cup of tea at about 3 p m Discontinuing this newly-acquired habit resulted in the prompt disappearance of the symptoms and it was noteworthy that, in his case, tea precipitated extrasystoles only when taken in the early afternoon whereas he could take a much greater quantity for breakfast without any ill effects.

frequency of this arrhythmia in healthy people; in others a short talk on the normal mechanism of the heart beat and the harmlessness of an occasional beat, arising elsewhere in the heart and momentarily interfering functionally with the rhythm, will be helpful. Some patients appreciate a simple explanation of the post-extrasystolic pause, as this allays the anxiety which many patients have because "the heart stood still for such a long time".

In most instances of this group it is advisable to await the effect of such explanatory talks before resorting to drugs. Sometimes the successful treatment of the anxiety caused by the arrhythmia results in the disappearance, or rarer occurrence, of the extrasystoles. But even if this is not the case, once the patient is reassured about the innocuous character of the irregularity, he soon learns to disregard the "missed beats" and no further treatment may then be necessary. A certain proportion remain, however, in which symptoms continue to be so troublesome that an attempt should be made to abolish the extrasystoles by pharmacological means In such cases quinidine is the drug of choice and its successful early use, preferably for a short time, is also of great psychological importance, since it demonstrates to the patient that means are available to rid him of his troubles Details of quinidine treatment are given below.

2. *Treatment of Extrasystoles because of their great numbers, in the* **absence of any other Pathological Condition**

In this group drug treatment of the condition is usually necessary, not only because symptoms are more pronounced, but also because very numerous extrasystoles may have the same effect on the general circulation as more pronounced tachycardia, namely, reduced cardiac output with all its consequences Such great numbers are, however, more fre-*quently found in association with other pathological conditions, as discussed immediately* below

3. Treatment of Extrasystoles occurring in association with certain other Pathological Conditions

In a certain proportion of cases of this group the arrhythmia is found to be precipitated by, *or at least associated with, some extracardiac* pathological condition, for example, chronic gall-bladder disease, hyperthyroidism, anxiety state, etc. In such instances treatment of the underlying condition obviously is the appropriate approach.

Regarding the treatment of extrasystoles in *cardiac* patients, two main considerations determine the indication of treatment of extrasystoles:

(*a*) An associated pathological condition in which extrasystoles are known often to be precursors of fibrillation, namely, auricular extrasystoles of auricular, ventricular extrasystoles of ventricular fibrillation; and

(*b*) Structural myocardial disease in which, apart from (*a*), the additional impairment of cardiac function produced by the arrhythmia calls for its treatment.

Conditions in which *auricular* extrasystoles are known frequently to be precursors of auricular fibrillation are mitral valvular lesions and coronary disease In these two conditions treatment of the arrhythmia is indicated if only to postpone the onset of auricular fibrillation Auricular extrasystoles occurring in myocardial infarction call for prompt treatment for the same reason; they may be associated with other auricular arrhythmias and, to a certain extent, may indicate possible auricular infarction (see section on "Coronary Disease"). Multiform *ventricular* extrasystoles occurring in coronary or myocardial disease always call for immediate treatment as they are an unequivocal danger signal of threatening ventricular fibrillation. This is particularly important if they occur after an attack of myocardial infarction *More numerous ventricular extrasystoles arising from the same*

focus, occurring in coronary or myocardial disease or after myocardial infarction, have to be treated for the same reason ; moreover, in such conditions the extrasystolic arrhythmia further impairs the already reduced cardiac efficiency and for this reason, too, every effort has to be made to regularize the cardiac rhythm by drug treatment. Regarding extrasystoles due to digitalis, see p 283

amide, which has recently been introduced, may well acquire special importance.

Quinidine

Regarding the mode of action of this drug and a discussion of experimental and clinical observations see section on "Quinine and Quinidine."

In connexion with the clinical employment of quinidine, which in the vast majority of cases is given by mouth as quinidine sulphate, two points should be emphasized : some

occur (*see* below) systematic treatment is started the following day The individual dose, as well as the spacing of the doses, has to be adjusted according to the patient's individual reaction and requirement which vary widely As initial doses we recommend :

0 2 gramme thrice daily in the treatment of troublesome extrasystoles in otherwise healthy individuals ;

0 2 gramme four-hourly in the treatment of extrasystoles of the above groups (2) and (3).

The effect of the drug can usually be assessed within twenty-four hours. The subsequent optimum dose is the smallest effective individual dose given at the longest intervals without the persistance, or re-appearance, of the arrhythmia Thus, if with initial doses given as indicated above, extrasystoles occur before the next dose is given, the drug should be administered at shorter intervals , if the individual dose of 0 2 gramme is inadequate to suppress the ectopic beats, larger doses, for example, 0 4 and in some rare cases even 0 6 gramme have to be given

Once cardiac rhythm has become regular it is advisable to continue the exhibition of quinidine for about one week in the same minimum dosage and at the same maximum intervals which have proved effective Subsequently the number of daily doses is gradually reduced, and if the individual single dose exceeded 0 2 gramme, this also is gradually decreased It is common experience that, with this method, extrasystoles remain in abeyance even if the drug is finally discontinued This is, however, not always the case Should they recur in an otherwise healthy subject it is often not necessary to re-institute the drug, since the patient has learned to disregard the occasional "missed beats". But if the arrhyth-

deafness and urticaria A host of others have been observed, but they are less common, for example, abdominal pain (Jamieson), headache and dizziness, marked rise in temperature (Sturnick), blurring or mistiness of vision (Clark-Kennedy), photophobia, diplopia, scotomata, even temporary blindness (Jezer and Schwartz) and optic atrophy Pruritus (Wolff and White) and exanthemata (papular or scarlatiniform, Clark-Kennedy) have been observed, also sweating, fullness in the head, flushes, excitement, confusion and, rarely, syncope Gordon *et al* reported apnoea and respiratory paralysis with collapse,

and Licciardello and Stanbury observed acute haemolytic anaemia. Occasionally the drug produces intraventricular block (White, Marvin and Burwell) or ventricular tachycardia (two such instances were reported by Wolff and White). Any of these signs of cinchonism calls for discontinuing the drug. Whether, after the subsidence of toxic symptoms, the drug should be re-instituted must be judged individually and much must be left to the physician's experience and judgement

Quinidine is certainly the most efficacious drug for the suppression of extrasystoles though not effective in every case (Deschamps; Lian and Blondel). Smith (1922) found a marked reduction in the number of extrasystoles in seventeen out of twenty patients, that is in 85 per cent., and Barrier reported a similar proportion (90 per cent.) of successes in his cases. *Our personal experience is in agreement with this figure.*

In one instance of ventricular tachycardia following myocardial infarction Levine and Stevens found it necessary to give 1 5 grammes of quinidine five times daily in order to abolish the arrhythmia. This report is quoted as an instance of an exceptionally large dose. In cases of this kind procaine amide may well take the place of such excessive doses of quinidine

The intravenous administration of quinine, introduced in the treatment of extrasystoles by Hecht and Zweig (1917) and later advocated by Singer and Winterberg (1922), is rarely necessary and the same holds good for the intravenous use of quinidine sulphate (0 2–0 4 *gramme in 10 0 cc, to be given very slowly, or as a drip infusion). This method is not free* from risk sudden collapse may occur, particularly in patients with myocardial disease if the injection is given too quickly, and even small doses of quinine or quinidine given intravenously to patients with heart block have caused ventricular fibrillation (Schwartz and Jezer, Smith *et al.*, 1940, Sagall *et al*). Collins recommended the intravenous administration of quinidine lactate in doses of 0·2–0 4 gramme for the treatment of acute arrhythmias, including extrasystoles, during clinical anaesthesia The nature of the arrhythmias was, however, diagnosed " entirely on clinical grounds ".

It cannot be denied that in certain emergencies, for example numerous or multiform extrasystoles and ventricular tachycardia complicating myocardial infarction or occurring [illegible]

[illegible]

Digitalis

In normal subjects digitalis preparations abolish extrasystoles in a large proportion of [illegible]

and more specific regarding the suppression of ectopic beats, and the drug is far more [illegible]

signifying the presence of the dreaded disease; however well reasoned the physician's explanation may have been, the result of the prescription will be that the patient comes to doubt the assurance and to distrust the physician.

The two conditions in which we recommend to use digitalis for the suppression of extrasystoles are:

(1) failure of quinidine to achieve the desired result, and

(2) an associated cardiovascular condition in which digitalis is indicated, for example, congestive heart failure.

Regarding (2) it should be stressed that the presence of extrasystoles in congestive heart failure not only is no contra-indication against its use, but an additional indication. Not

[illegible]

indication, the latter call for great caution in the further exhibition of the drug, in most cases necessitating reduced doses and often discontinuing the drug, at least temporarily (see section on "Digitalis").

In some instances great discrimination in deciding whether, or in what dosage, digitalis should be continued is required. Thus, in a woman of forty-seven with Lutembacher's syndrome, at first sinus rhythm with occasional ventricular extrasystoles was present; subsequently auricular flutter developed with occasional extrasystoles. Soon after digitalis treatment had been started with the object of converting flutter into fibrillation, coupled beats were recorded due to one ventricular extrasystole following each conducted beat. Contrary to the generally accepted rule it was decided in that case to continue with digitalis, though temporarily to reduce the dose, since extrasystoles were known to have occurred

[illegible]

tachycardia. The further development showed this assumption to have been correct; with further judicious use of digitalis the number of extrasystoles decreased and conversion into auricular fibrillation was achieved on the eighth day of digitalis treatment (Schott). It should be emphasized that such cases are rare exceptions. In most cases the occurrence, during digitalis treatment, of extrasystoles in any but the smallest numbers calls for temporarily discontinuing the drug

The employment of digitalis in "very small doses" for the treatment of extrasystoles

[illegible]

lanata, in doses of 0 25 mg. three times a day initially, once or twice a day subsequently If digitalis is given to patients with congestive heart failure and extrasystoles the dose depends on the underlying condition Whatever preparation is given the patient must be kept under supervision because of the possible occurrence of signs of digitalis intoxication The most important ones are anorexia, nausea and vomiting, and the re-appearance of extrasystoles after they had been abolished, also ectopic ventricular tachycardia If digitalis is taken for longer periods, yellow vision and drowsiness (resembling pre-uraemia) may be the first signs of drug intoxication.

[illegible] ventricular in

c [illegible]

[illegible], quinine (or quinidine) and strychnine was popular. It was known as "Wenckebach's pills", which contained quinidine sulphate 0 04 gramme, digitalis (powdered leaves) 0 02 gramme,

strychnine nitrat. 0·0006 gramme. The usual dose was 3–6 pills daily. The efficacy of strychnine for this purpose seems questionable (see section on "Strychnine").

Other Drugs

The drugs briefly discussed below have all occasionally been used successfully in the treatment of extrasystoles, but, with the possible exception of the recently introduced procaine amide, their effect is far less constant and they have to be considered as much inferior to quinidine and digitalis. The pharmacological action of these drugs in relation to ectopic beats is discussed in the appropriate sections in the chapter on drugs, where it was shown that a great variety of compounds may cause as well as abolish extrasystoles. In the following paragraphs some supplementary remarks will be found on their clinical application.

Procaine Amide ("Pronestyl")

This drug has been introduced in the treatment of extrasystoles and ventricular tachycardia so recently that further investigations have to be awaited before its value can be assessed The reports so far available indicate that it is promising. The effective oral dose was found to vary widely in different patients. In patients with ventricular extrasystoles doses varying between 0·4 and 1·0 gramme, given either orally or intravenously, proved effective to suppress the arrhythmia for a period varying from a few minutes to many hours. In some cases the drug had to be given for longer periods and the suggested maintenance doses range from 0·5 to 1·0 gramme every three to six hours. This drug proved particularly effective in abolishing ventricular tachycardia (usual initial dose 1·25 grammes, followed in one hour by an additional 0·75 gramme if the tachycardia persisted). The chief side-effects were hypotension with the intravenous route, and nausea and vomiting with oral administration. If administered intravenously the drug must be given very slowly (100 mgm per minute or less) and with constant control of blood pressure and electrocardiogram For some further details and references see section on "Cocaine", p. 309.

Novocaine (Procaine)

In doses of 100 mgm, given intravenously, procaine has been successfully used in the treatment of extrasystoles occurring suddenly, and especially in that variety occurring during anaesthesia It has also been employed in extrasystolic arrhythmias occurring after myocardial infarction It seems fairly certain that procaine amide will supersede novocaine (procaine) in the treatment of such arrhythmias.

Potassium Salts

Potassium acetate, given as a 25-per-cent solution in peppermint water in doses of two to four grammes every four to six hours, has been recommended repeatedly, especially for the treatment of extrasystoles due to digitalis intoxication This method should be considered particularly in patients in whom quinidine or Pronestyl cannot be given because of intolerance to these drugs, especially in instances of digitalis extrasystoles. Impaired renal function is an important contra-indication

Physostigmine

was recommended by Hecht and Zweig in daily doses of 3 mgm. and is sometimes replaced by Prostigmine.

Atropine and Belladonna Preparations

were sometimes used and Laubry recommended them as late as 1933. It seems certain that such drugs may occasionally abolish extrasystoles, but the side-effects are by no means negligible.

Papaverine

Although this drug has been claimed to suppress extrasystoles, for the reasons discussed in the section on this drug (p. 335) we do not recommend its use for the sole purpose of treating extrasystoles.

Fagarine

which can only be given intramuscularly, cannot be recommended because of dangerous side-effects.

Epinephrine and Ephedrine

were occasionally employed, their use should be discouraged since more often than not they cause, rather than abolish ectopic beats.

SUMMARY

The great majority of patients with extrasystoles do not require treatment. Three main conditions are listed in which extrasystoles necessitate treatment.

(1) If in the absence of any other pathological condition they give rise to symptoms of clinical importance, physical or psychological,
(2) If they are very numerous,
(3) If they occur in association with other pathological conditions in which they may initiate auricular or ventricular fibrillation, or may further impair cardiac function.

Regarding the above group (1) the importance of taking the patient's complaints seriously and of carrying out a complete examination is emphasized. Attention in great detail must be paid to the patient's mode of life, some re-adjustment of which often ensures successful treatment of the arrhythmia. In many cases no precipitating factor can be found; [illegible]

In the above group (2) drug treatment of the premature beats is usually necessary because of the severity of symptoms and of the frequent impairment of circulatory efficiency caused by the pronounced arrhythmia.

Regarding the above group (3), in some cases the extrasystolic arrhythmia is found to be associated with, or precipitated by, an extracardiac condition, in such instances treatment [illegible]

is discussed in some detail. Amongst other drugs recommended for the treatment of

extrasystoles procaine amide seems promising, particularly in the treatment of ventricular extrasystoles and ventricular tachycardia, but the result of further investigations has to be awaited before its value can be assessed. This holds good particularly in regard to the relative merits of procaine amide and the intravenous use of quinidine in emergencies. Other drugs briefly discussed are novocaine, potassium salts, physostigmine, atropine and belladonna preparations, papaverine, fagarine, and epinephrine and ephedrine. Of these, potassium salts seem to deserve consideration; novocaine has been superseded by the recently-introduced procaine amide. The remaining ones cannot be recommended and the use of fagarine, epinephrine and ephedrine in the treatment of extrasystoles should definitely be discouraged.

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CHAPTER XII

THE MECHANISM UNDERLYING THE ORIGIN OF EXTRASYSTOLES AND OF ECTOPIC AUTOMATIC BEATS

INTRODUCTORY REMARKS

The discussion in the various chapters of this book will have made it apparent that the mechanism underlying the different forms of ectopic arrhythmias varies Thus, in dissociation with interference, beats giving the impression of being extrasystoles were shown actually to be sino-auricular ones, interfering at times with an otherwise regular A-V rhythm Return-" extrasystoles " can be assumed to be due to two successive activations of the ventricles by the same impulse In parasystole the co-existence of two centres exhibiting automatic impulse formation can be considered established. Other instances of arrhythmias simulating the presence of extrasystoles were mentioned in the chapter on " Coupling ".

None of the above mechanisms is, in our opinion, responsible for those ectopic beats which are *extrasystoles* in the strict sense of the term as used in this book, namely, *ectopic beats with accurate coupling to the preceding beat* In the present chapter their mode of origin will be discussed and their relationship to automatic beats considered In doing so we hope to substantiate our contention that this variety of ectopic arrhythmias should be separated from the others

It seems to us that a discussion of this subject touches upon several aspects of great physiological importance, while in view of the common clinical occurrence of extrasystoles it should not be without some clinical interest.

It has to be admitted at the start that our knowledge about this problem is very scanty. As long as the mechanism of the normal cardiac impulse formation is incompletely understood, our knowledge about that of the more complicated ectopic ones is of necessity very imperfect—to say the least. We believe, however, that recent advances in physiology make it possible to obtain a somewhat clearer picture of the underlying processes than had previously been the case

Our thesis is that true extrasystoles are precipitated in the ectopic centre by the preceding beat and are thus a passive, derivative phenomenon, as distinct from those forms of ectopic arrhythmias (for instance parasystole) in which two independent automatic centres, of equal importance, of impulse formation co-exist, the activity of neither of which is deriving from that of the other

Our thesis, stated in this form, is, from one point of view, the reverse of what was held by some of the most competent authorities not so long ago. we refer to the conception that

and Winterberg, 1927), this latter group was thought to occur " passively " as the result of failure of normal beats to be initiated or to be conducted This is one aspect of the conception, then held already for some time by several authorities, that there was a fundamental differ-

as distinct from nomotypic (Hering, 1911). But Lewis himself, under the influence of Kaufmann and Rothberger's work on parasystole, became doubtful about this distinction and in the third edition of his book (1925) stated that he was "unable to rewrite with sufficient confidence those distinctions between homogenetic and heterogenetic impulses which I emphasized in the last edition of this book". That such a distinction, though in a different way of application, is in fact justified in our opinion will be shown in this chapter.

The idea that extrasystoles with accurate coupling are precipitated by the preceding beat is, of course, an old one. But much controversy has existed regarding the strict separation of this group and its relationship with others. Some of these views will first be discussed.

ALTERNATIVE HYPOTHESES

Extrasystoles and Parasystole

At one time attempts were made to explain *all* ectopic arrhythmias on the basis of a parasystolic mechanism, and extrasystoles with accurate coupling were thus also considered to be due to the independent activity of an ectopic centre, that is, to be automatic in origin. In the chapter on pararrhythmias reasons were given why this view is untenable. The main arguments may here be summarized by recalling that two of the three main features of parasystole are absent in the common variety of extrasystoles, namely, varying coupling of the ectopic beats and the occurrence of combination (= fusion) beats. The further hypothesis that the accurate coupling of the extrasystoles is due to a tendency of the normal and of the—presumed automatic—ectopic rhythms to occur in simple mathematical relations to one another (Kaufmann and Rothberger, 1922) was an obvious *petitio principii* and this relationship could be shown to be the *result*, and not the *cause*, of the accurate *coupling of the extrasystoles.*

With rare exceptions (for example Schaefer, 1951), the view that extrasystoles are due to a parasystolic mechanism has now generally been abandoned and it is significant that Rothberger, its most important protagonist at one time, finally gave it up himself (Rothberger, 1932).

Circus Movement and Re-entry Mechanism

The theory of circus movement, widely accepted until recently as an explanation of the mechanism of auricular fibrillation and flutter, though seriously called in question of late, [illegible]

this condition, a wave of excitation is assumed to circulate in certain pathways of the excitable tissue, the same impulse thus activating successive portions of the heart muscle again and again.

A mechanism of this kind is, in our opinion, a satisfactory explanation of return extrasystoles only, but not for the common variety of extrasystoles with accurate coupling. Before giving our reasons for this statement it is opportune briefly to discuss the work on which that theory was based.

Two observations formed the main basis for the belief that extrasystoles were due to the re-entry of the impulse which had produced the preceding, that is initiating beat.

The first is that a single stimulus, applied at the end of the refractory phase, may precipitate two or more successive contractions

The first to report such a phenomenon in the heart were Marchand and Munk, both in 1878. Marchand found that one make shock applied to the A-V border of a frog's hear

produced several contractions, increasing in number up to thirty with increasing intensity of the stimulus; Munk, also in the frog's heart, saw a series of pulsations after a single mechanical stimulation and also noticed that the sequence of contractions of the various portions of the heart varied according to the site of the mechanically stimulated part of the heart—an early clear description of an ectopic rhythm. Other early observations of several contractions being elicited by one stimulus include those on the bulbus of the frog's heart by Engelmann (1882), also Lovén's findings (1886) that a single induction shock applied to the auricle of the frog's heart yielded two, or rarely three, contractions provided the stimulus was timed to fall within 0 1 second after the maximum of systole; the period, lasting about 0 1 second, during which this phenomenon occurred Lovén called " kritische Periode " (critical period), a term which was to gain increasing importance with the investi-

precipitate a series of contractions Andrus's observation of a—presumably heterotopic—auricular rhythm following one forced auricular contraction in certain circumstances may be another instance.

The first to consider this phenomenon to be due to a kind of re-entry of the impulse and to consider the possibility of its being responsible for extrasystoles seems to have been Mines (1913, 1914). The phenomenon of several contractions following one stimulus was extensively studied by de Boer (1921) and his observations were confirmed on the dog's auricle under vagal stimulation by Lewis, Drury and Iliescu. De Boer was the main pro-

refractory periods where, he believed, the excitation wave became temporarily arrested while at the same time still being capable of exciting other neighbouring structures. The result of all this was thought to be a return of the excitation to a point whence it had started and which had become excitable again. Valid objections against this theory were soon put forward, summarized in detail by Wenckebach and Winterberg (1927, p 537) and by Rothberger (1931, p. 680)

Wiggers)

there producing locally unidirectional block in the direction from conducting system to myocardium. In such circumstances the excitation wave is assumed to enter the nearby myocardium from the penultimate twig only by other branches, but be conducted backwards through the affected twig. If, during that time, the adjacent myocardium had become excitable again, the excitation wave could then produce a second contraction. Ashman and Hull base their views on the above findings of Schmitt and Erlanger. While such a mechanism cannot be disproved, just as in our opinion it has not been proved, we do not consider it an acceptable explanation for the common variety of extrasystoles for various reasons Of these, the most important one will become apparent in the succeeding parts of this chapter, namely, that the mechanism which we put forward is supported by a wealth of physiological observations on the initiation and conduction of impulses in various tissues, including the heart, whereas the assumption of a circus movement based on that of a hypothetical area of unidirectional block is based only on findings in very special experimental circumstances obtained on strips of cardiac muscle and then, without any further proof, applied to the most peripheral branches of a highly specialized tissue, that is the Purkinje strands The observations of Schmitt and Erlanger can themselves be interpreted *in other ways, without postulating a circus movement according to Bozler (1943a) the* second contraction is due to [illegible] phases of the afterpotential [illegible]

Other difficulties are ment [illegible] that their explanation of such difficulties is wholly convincing In particular, their statement that the island of depressed tissue need not be very large and that therefore the premature beat produced by the mechanism favoured by them " would appear as if it originated in a focus " seems to us to evoke an unjustifiable assumption· if the assumed area of depressed tissue is so small that origin in a focus of the extrasystole appears to occur, it seems far more likely to base the explanation on such focal origin. This is what we propose to show as actually occurring. Our view is also supported by more recent observations on the effect, upon extrasystolic impulse formation, of warming or cooling of the focus of origin in such instances in which true extrasystoles were elicited by the topical application of various compounds: it seems most unlikely that such application creates an area of unidirectional block which responds invariably and instantaneously to warming and cooling of the focus in the way which is described in various places of this book. Also, the action of the systemic exhibition of drugs and of emotional factors upon extrasystoles is far more likely to be due to the effect of such factors upon the local conditions of the ectopic focus, known to be susceptible to nervous influences and to be unstable, than to an influence on a (hypothetical) area of unidirectional block This, too, will, we hope, become apparent in the course of the subsequent parts of this chapter.

The second observation assumed by Lewis (1925) and Wenckebach and Winterberg (1927) to support the theory of a re-entry mechanism being responsible for extrasystoles is at first sight more convincing. It concerns an observation of Lewis, Feil and Stroud who noticed in the dog's auricle that after stimulation by rapid induction shocks some after-effects in the form of flutter often extended beyond the end of stimulation. In one experiment such after-effect consisted of one beat only, which was followed by a short period of coupled beats (auricular bigeminy) These authors argued that, if the one beat constituting [illegible]

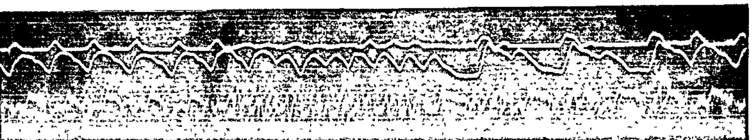


FIG 202 —From an experiment on a dog Tracings from above downward signal (stimulation), suspension curves of right auricle and right ventricle, electrocardiogram (ano-oesophageal lead), time base 0 02 second For explanation, see text From SCHERF, 1926, *Z ges exp Med.*

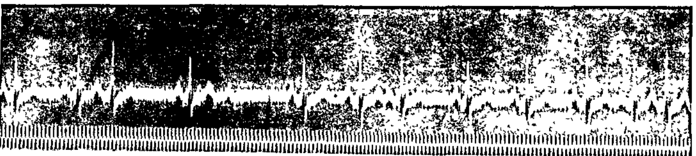


FIG 203 —From a woman of thirty-six with attacks of paroxysmal tachycardia Note, after the third sinus beat, two P waves at an interval of 0 2 second Time base 0 04 second For further explanation, see text

occurred. After the end of this auricular tachycardia the P-R interval was lengthened from the previous 0 06 to 0 08 second. The first two A-V beats were followed by two premature P waves, the third one by only one, the interval between the two P waves following in short succession corresponding to a rate of 650 per minute. (The auricular contractions corresponding to those P waves can also be traced in the suspension record.) The shape of these P waves resembled that of some of those occurring during stimulation, and if more persistent flutter occurred in this experiment it showed P waves of the same shape. Later, similar arrhythmias were obtained by the topical application of aconitine or acetylcholine.

A comparable tracing was recorded in a clinical instance (Fig. 203). The patient, a thirty-six-year-old woman without any evidence of structural heart disease, suffered from attacks of paroxysmal auricular tachycardia, flutter and fibrillation. In Fig. 203 several auricular extrasystoles are seen, some of them occurring early in diastole and showing aberrant intra-ventricular conduction Following the third sinus beat, two premature P waves were recorded, the first of which is superimposed on the T wave of the preceding beat. The interval between these two P waves is 0 2 second, corresponding to a rate of 300 per minute. Here again, the mechanism underlying the origin of these two P waves occurring in quick succession can be considered to be rudimentary flutter.

While we believe that such arrhythmias are, in fact, rudimentary flutter we do not think that they can be interpreted as being due to a circus movement. The argument of Lewis, and of Wenckebach and Winterberg was since flutter is due to a circus movement, and since the above arrhythmias are rudimentary flutter, down to one ectopic beat of a bigeminal group, such ectopic beats must therefore also be due to a circus movement. As however, for reasons fully discussed in the sections on flutter and fibrillation, we believe flutter to be due, not to a circus movement, but to a repetitive impulse formation in an ectopic centre, the above reasoning of Lewis, and of Wenckebach and Winterberg has been deprived of its basic rationale, and we interpret the instances of rudimentary flutter, described above, as due to ectopic focal impulses

In addition to this, there are valid objections against the assumption of extrasystoles being due to a circus movement Apart from those discussed above in connexion with Ashman and Hull's views, the length of coupling of some extrasystoles, particularly of auricular ones, is a great stumbling-block which was also realized by Lewis (1925): he pointed out that there is no path in the auricles of sufficient length for a circulating wave of excitation to move during such interval—and such continuous movement is, of course, a *conditio sine qua non* for assuming such a mechanism.

IMPULSE FORMATION IN AN ECTOPIC CENTRE

If our contention that auricular flutter and fibrillation are due to the rapid stimulus formation in a single centre, or several centres respectively, is correct, a closer resemblance of these arrhythmias to extrasystoles would be established than had hitherto been assumed. For one of the more important conclusions of earlier studies on extrasystolic arrhythmias was that extrasystoles originate in a circumscribed focus. The foundation of this view—which also made it possible to exclude re-entry (or circus movement) mechanism regarding extrasystoles—warrants some more detailed discussion.

The Origin of Extrasystoles in One Circumscribed Focus

The fact that extrasystoles may originate in *one* circumscribed focus was experimentally demonstrated in the following way.

In experiments on the dog's heart *in situ* it could be shown that, after the injection of quinine for the purpose of avoiding ventricular fibrillation, electric shocks applied to any

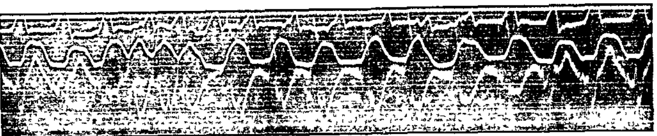


FIG 204 —From an experiment on a dog Significance of the individual tracings as in Fig 202 For explanation, see text From SCHERF, 1926 *Z ges exp Med*

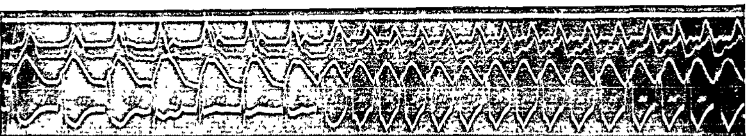


FIG 205 —From an experiment on a dog Tracings from above downward Signal (stimulation), suspension curves of right auricle, left auricle, right ventricle, electrocardiogram, time base 0 02 second Re-appearance of ectopic beats at a greatly increased rate resulting from warming their site of origin For further explanation, see text From SCHERF, 1927 *Z ges exp Med*

part of the ventricular surface caused series of ectopic beats to occur after the end of stimulation. The additional administration of small doses of barium—too small to cause any changes in the electrocardiogram—facilitated the onset of such ectopic arrhythmias.

Fig. 204 was obtained from a dog, anaesthetized with ether, shortly after the injection of 0 2 gramme of quinine. As the left bundle branch had been severed, the ventricular complexes of the first two beats show the typical bundle branch block shape. Four ectopic beats were elicited by stimulation of the right ventricle with induction shocks. (The first coincided with a sinus beat and showed a combination complex of almost normal shape.) Following these four forced beats a series of seven consecutive abnormal complexes were observed, having a similar shape and assumed to originate in the previously stimulated centre. Such series were occasionally much longer, comprising as many as thirty beats (Scherf, 1926)

The view that such ectopic beats originated in the stimulated centre was strongly supported by the observation that warming the site of former stimulation resulted in an increase in rate of the ectopic beats. Fig 205 is taken from such an experiment. A long series of ectopic beats had occurred in a dog, sensitized with barium, after electrical stimulation of a circumscribed area on the surface of the right ventricle. Fig. 205 shows the last three ectopic beats of this series, followed by four beats of the basic (A-V) rhythm; subsequent warming of the ectopic focus brought out again the ectopic rhythm with an increased rate (Scherf, 1927).

More recently it has been found that extrasystoles with accurate coupling can experimentally be produced by the focal epicardial application, or sub-epicardial injection, of solutions of barium or sodium chloride, or of digitalis (see appropriate sections) As is pointed out there, such experiments tended to show that the extrasystoles originated in a circumscribed focus, namely, the site of application of the compound. Here it may be added that the instantaneous suppression of the extrasystoles by cooling the site of origin, and their immediate appearance by its warming in certain experimental conditions, are further observations which make the assumption of a local circus movement most unlikely, to say the least (*see* Scherf, 1942) Fig 206 reproduces some relevant observations.

Fig. 206a is taken from an experiment in which a 10-per-cent. solution of sodium chloride had been injected sub-epicardially into a small area of the conus of the right ventricle. While this injection alone did not produce any arrhythmia, the recorded bigeminal action ensued immediately on warming the site of injection by a thermode

Fig. 206b illustrates the converse phenomenon. focal application of 0 1 cc. of a 0 1-per-cent. solution of ouabaine to the apical region of the left ventricle had yielded the arrhythmia reproduced at the beginning of the record, namely, two or three left-ventricular extrasystoles following each sinus beat. Cooling of the site of application immediately abolished the arrhythmia (second part of the record). This phenomenon could at will be reproduced several times.

Fig. 206c shows, in its first portion, auricular bigeminy. The sinus beats are characterized by tall, peaked P waves; each is followed by an auricular extrasystole, the P waves of [illegible]

is shown in the latter portion of Fig. 206c. Beginning and end of warming are indicated in the record by arrows; the ventricular tachycardia started two seconds after the beginning, and terminated 1·6 seconds after the end of warming

The production, by means of barium, strophanthin and aconitine, of various forms of arrhythmias, including bigeminy, in isolated strands of Purkinje tissue (Wachstein) may

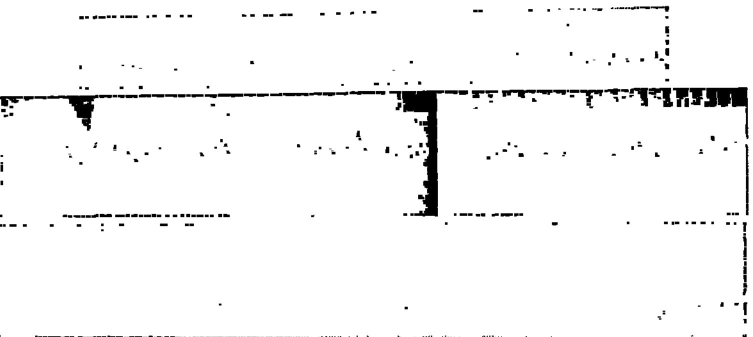


FIG 206.—From experiments on dogs *a* Bigeminal rhythm precipitated by warming the site of sub-epicardial injection of sodium chloride (conus of right ventricle) *b* The first part of the record shows two or three left-ventricular extrasystoles precipitated by the focal application of 0 1 cc of a 0 1 per cent solution of ouabaine to the apical region of the left ventricle The second part of the figure shows abolition of the ectopic arrhythmia by cooling the site of application of ouabaine *c* The first part shows auricular bigeminy elicited by the sub-epicardial injection of strophanthin into the middle portion of the sinus node The later part of the figure shows a right ventricular ectopic tachycardia precipitated by warming the site of the previous sub-epicardial injection of strophanthin into the conus area of the right ventricle Beginning and end of warming indicated by arrows For further explanation, see text

briefly be mentioned as further supporting the view that such contractions originate in a circumscribed focus.

The Dependence of Extrasystoles upon an Initiating Beat

While the investigations discussed so far demonstrated that ectopic beats arise from a circumscribed focus, they did not provide any information as to the mechanism underlying the common variety of extrasystoles with fixed coupling. The essential difference between the above experimental and the clinical arrhythmias was that, in the former, ectopic beats were elicited by some local experimental interference and—with the exception of those due to the topical application of certain compounds—were not accurately coupled to the preceding beat, whereas in the latter the extrasystoles follow the initiating beat with accurate coupling and without any artificial localized stimulation. The argument was therefore always possible, and perhaps justified, that the above experimental arrhythmias were due to increased automaticity of an ectopic centre, and that conditions prevailing in such arrhythmias were qualitatively different from those in true extrasystolic arrhythmias about the nature of which they did not yield any conclusive information.

This problem became accessible to experimental investigation when it was found by Scherf in 1929 that true extrasystolic arrhythmias could experimentally be produced by means of the systemic application of aconitine. This made it possible to show that extrasystoles are caused by the preceding beat. Such arrhythmias resemble in every way the common clinical variety, the extrasystoles having in the electrocardiogram constant shape, and accurate coupling to the preceding beat. Arrhythmias of this kind are produced by aconitine only if this is given in a special way, the details of technique being described in the chapter on "Extrasystoles and the Nervous System" (*see* p. 255). All authors who had previously studied arrhythmias caused by aconitine obtained only irregular ectopic arrhythmias, soon changing into ventricular fibrillation, if bigeminal rhythm occurred at all it extended only through a few cycles. This fact deserves to be briefly mentioned in view of some misleading statements recently made in this connexion. See section on "Flutter and Fibrillation", p. 228.

If aconitine was administered according to the method published by Scherf (1929), not only isolated extrasystoles, but also long chains of bigeminal heart action due to extrasystoles could be produced; this made it possible to demonstrate that the extrasystoles were precipitated, in the ectopic centre, by the preceding beat and were not due to an independent automaticity of the centre. This was shown in several ways.

(1) If, during a continuous bigeminy, a forced (ventricular or auricular) contraction was elicited by a mechanical or electrical stimulus, such forced contractions were followed by the same extrasystoles as were the normal beats before such stimulation.

Fig 207 illustrates this condition. As a result of aconitine action trigeminal rhythm was present, one sinus beat being followed by two ventricular extrasystoles arising in the left ventricle. On two occasions (the fourth and the tenth beat of the record) a forced beat of the right ventricle was precipitated by mechanical stimulation and these were followed by the same couple of left-ventricular extrasystoles as were the sinus beats. With manifold variations of this experimental procedure it could be shown that, whenever during bigeminal or polygeminal rhythm a forced beat was elicited, it was invariably followed by the same extrasystoles as were the sinus beats. Irrespective of where such forced beats were produced, whenever their excitation spread over the heart they precipitated extrasystoles in the same centre of extrasystolic impulse formation

of the path which the initiating impulse had to traverse in order to reach the centre of

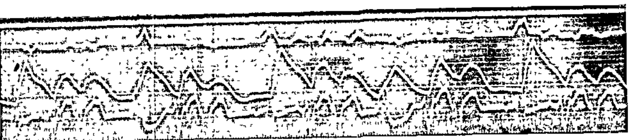


FIG 207—From an experiment on a dog Significance of the individual tracings as in Fig 202 Trigeminal rhythm due to aconitine, one sinus beat being followed by two left-ventricular extrasystoles The fourth and tenth beats are ectopic beats precipitated in the right ventricle by mechanical stimulation These forced beats are followed by the same couple of left-ventricular extrasystoles as are the sinus beats The length of the coupling of the first extrasystole depends on the site of origin of the preceding beat For further explanation, see text From SCHERF, 1930a *Z ges exp Med*

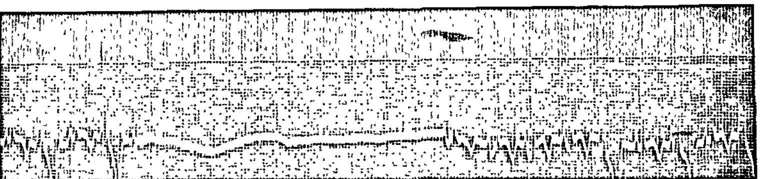


FIG 208—From an experiment on a dog Lead 2 The beginning of the tracing shows bigeminal rhythm due to the topical application of 0 05 cc of strophanthin into the conus area of the right ventricle Faradic vagal stimulation produced cardiac standstill without any automatic beats From SCHERF, 1944 *Exp Med Surg*

extrasystolic impulse formation, thus proving that impulse formation in this centre does, in fact, depend on an initiating beat. This is illustrated by the same Figure 207.

Extrasystoles experimentally produced by aconitine have an absolutely constant coupling as long as they follow the same kind of initiating beat. If, however, the site of origin of the initiating beat varies, the length of coupling of the extrasystoles varies in a systematic way. Thus, in Fig. 207, the coupling of the first extrasystole following a sinus beat was invariably 0 31 second as compared with 0 35 second of those same (left-ventricular) extrasystoles following beats forced from the *right* ventricle. If, in the same experiment, beats were forced in the *left* ventricle, the coupling of the extrasystoles after such beats was 0 29 second. In this experiment the extrasystoles always originated in a focus in the left ventricle, whenever they followed a beat forced in the contralateral ventricle their coupling was 0 03–0 04 second longer, and when following a forced beat of the ipsilateral ventricle, was 0 01–0 02 second shorter, than the coupling of those premature beats which followed sinus beats This observation indicates that the length of the coupling depends *inter alia* on the length of the path which the initiating impulse has to traverse in order to reach the extrasystolic centre (Scherf, 1930, a) The difference in the lengths of coupling accords well with the interval required for an impulse to spread from one ventricle to the other (Eppinger and Rothberger, Lewis and Rothschild) Similar observations regarding the length of the path of an impulse being responsible for the interval between two contractions were made by Bethe (1937) on strips of the umbrella of medusae (Cotylorhiza).

(3) If, during bigeminal rhythm due to aconitine, bundle branch block lesions were produced, similar systematic and analysable changes in the coupling of the extrasystoles were seen. Such observations, described in the chapter on "Coupling" (p. 195), led to the same conclusions as set out under (2).

Extrasystolic and Automatic Impulse Formation

The work, reviewed so far, can be said to have established that extrasystoles are precipitated by the preceding beat, that they originate in a circumscribed focus and that they are not due to re-entry (circus movement) of the initiating impulse.

The question can now be discussed whether extrasystoles are due to increased automaticity of the ectopic centre, or whether, as we believe, extrasystolic impulse formation should be separated from the automatic one. This problem may be approached from two different angles. a critical review of the arguments put forward to claim an identical mechanism, and observations supporting the separation of extrasystolic from automatic impulse formation.

The first approach has already been discussed earlier in this chapter under the heading of "Extrasystoles and Parasystole". For co-existence of an ectopic *automatic* centre of impulse formation with a normal pacemaker is the hallmark of parasystole and it was stated above, as well as in the chapter on "Pararrhythmias", that attempts were made to explain, by such mechanism, extrasystoles with accurate coupling. Reasons were given why this view is untenable and the arguments need not be repeated here which preclude the application of a parasystolic mechanism to the explanation of extrasystoles

The second approach refers to observations on true extrasystoles which showed absence of increased automaticity, thus supporting the distinction between these two forms of ectopic impulse formation.

One impressive example is contained in the experimental investigations of Goldenberg and Rothberger (1931) on strophanthin arrhythmias. In experiments on dogs arrhythmias were produced by the intravenous injection of strophanthin combined with the inhalation of a mixture containing 25- or 30-per-cent. CO_2 in O_2 By this technique various ectopic arrhythmias could be produced, including bigeminal rhythm with accurately coupled

extrasystoles, polygeminy and ectopic tachycardias. If, in such experiments, the vagus was stimulated the result was cardiac standstill through several seconds (in one experiment 14 06 seconds!), during which only very occasional idioventricular automatic beats were observed which usually had a shape different from that of the extrasystoles. This observation proves that there was no vestige of increased automaticity of the ventricles in conditions where extrasystoles were numerous and that, therefore, these two forms of ectopic beats must be due to separate mechanisms. Such suppression of ventricular activity by vagal stimulation cannot, of course, be a direct vagal effect, for it is known that, in the mammalian heart, such vagal influence does not extend to the ventricles. These same experiments of Goldenberg and Rothberger contain a further proof of this, if proof were needed, for vagal stimulation was of no effect if applied during an ectopic tachycardia and produced standstill only after its termination, that is by inhibiting the next sinus beat With the suppression of the sinus beat the extrasystoles also failed to occur, thus proving their dependence on an initiating beat. A similar observation was made by Schott in rabbits

Another convincing example was found in experiments on arrhythmias following the *topical* application of strophanthin by means of sub-epicardial injection (Scherf, 1944) As pointed out in the section on " Digitalis ", by this method extrasystoles originating at the site of the injection can be produced As distinct from ectopic arrhythmias following

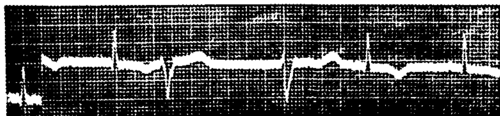


FIG 209 —Lead I A ventricular extrasystole is followed by an automatic beat of the same shape

the *systemic* administration of strophanthin, those elicited by *sub-epicardial* injection have all the characteristics of true extrasystoles Fig 208 is taken from such an experiment The beginning of the record shows bigeminal rhythm which had started five minutes after the injection of 0 05 cc. of strophanthin (Strophosid) into the conus area of the right ventricle Faradic stimulation of the right vagus produced cardiac standstill of nearly four seconds during which no signs of ventricular automatic beats were noted. After the end of vagal stimulation extrasystoles did not re-appear immediately when cardiac action was resumed, but only after the fourth sinus beat and then had the same shape and coupling as before.

These observations indicate, in our opinion, that the extrasystolic impulse formation, being dependent on, and precipitated by, an initiating beat, should be separated from automatic impulse formation which, by definition, is independent from any precipitating factor.

Occasionally, however, the same focus may give rise to extrasystolic *and* to automatic impulses Figs 209 and 210 provide examples.

Fig 209 was obtained from a seventy-four-year-old patient with coronary sclerosis. The second sinus beat is followed by an extrasystole with a coupling of 0 54 second, which, after an interval of 1 28 seconds, is succeeded by an automatic beat having the same shape as the extrasystole. What small differences there are in the features of these two beats are

most likely to be due to the combination of the second complex with a P wave which was due at about that time.

Fig. 210 illustrates another instance. It was recorded in a woman with mitral, aortic and tricuspid valvular disease and congestive heart failure. The underlying rhythm was auricular fibrillation with frequent extrasystoles, having a coupling of 0.40–0.44 second. On several occasions the first post-extrasystolic beat closely resembles the extrasystole so that origin in the same focus of such two beats has to be assumed. The small differences in shape between the extrasystolic and the post-extrasystolic (automatic) beats are attributable to the different lengths of the preceding intervals and the varying in superimposition of fibrillory waves. The most noteworthy feature of this record is that such automatic beats were, on their part, sometimes followed by extrasystoles of the same shape, their coupling being the same as that of extrasystoles following supraventricular beats (the first two couples of beats in the top, and the eighth and ninth beats in the bottom strip). (From Rachmilewitz and Scherf.)

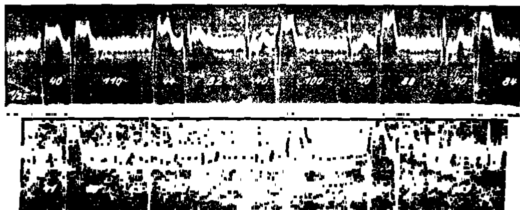


FIG 210 —Lead 3 The two strips are continuous Ventricular extrasystoles and automatic beats of the same shape For further explanation, see text. From RACHMILEWITZ and SCHERF *Z klin Med*

Similar observations of extrasystoles and automatic beats originating in the same centre were made experimentally (Rachmilewitz and Scherf) and, clinically, during carotid sinus pressure (Rihl) and during complete A-V block (Hoffmann, Christian, Scherf and Schott, 1932, Bloch). A tracing reproduced in a paper by Estapé shows this phenomenon in a patient with auricular fibrillation, though differently interpreted by the author. Such observations, as well as the rare transition from parasystole to extrasystoles of the same shape with fixed coupling (*see* chapter on "Pararrhythmias", p. 174) were believed by some to indicate an identical mechanism of these two forms of ectopic impulse formation. In our opinion this conclusion is not justified. Such observations indicate only that there is a focus of ectopic impulse formation which, in certain rare instances, is capable of both extrasystolic and automatic impulse formation. We visualize these two mechanisms to be qualitatively different in a way to be discussed below in this chapter. In the great majority of cases of ectopic arrhythmias only one of these two mechanisms is present in the focus. In the above instances both these mechanisms exist in the focus at different times, the quickest observed succession being found in the two cases of intermittent parasystole invariably starting with an extrasystole with fixed coupling, described by Scherf and Boyd. Furthermore, that extrasystolic impulse formation in a centre may predispose

hat centre to automatic impulse formation has been known for a long time from observaions on auricular extrasystoles it is by no means rare that the first post-extrasystolic beat has the same abnormal P wave as the extrasystole and sometimes this is observed in the first few post-extrasystolic complexes (see section on "Auricular Extrasystoles", p. 61).

While there are thus several kinds of observations illustrating a relationship, in some cases, between extrasystolic and automatic impulse formation, it should be emphasized that the total of such observations is very small as compared with the countless instances in which only extrasystoles or only automatic rhythms are encountered

PHYSIOLOGICAL PROCESSES UNDERLYING EXTRASYSTOLIC AND AUTOMATIC IMPULSE FORMATION

If it is desired to formulate some idea about the physiological processes underlying extrasystolic and automatic impulse formation such views have to be consistent with the observations that

(1) these two varieties of ectopic beats mostly occur independently from one another, whereby extrasystoles are commoner than ectopic automatic beats or automatic rhythms, and

(2) in some, comparatively rare instances these two varieties of ectopic beats have been *observed to be related to one another in various ways, for instance, a centre of extrasystolic* impulse formation producing, at times, automatic beats; automatic beats being followed by extrasystoles originating in the same focus, parasystole changing into extrasystolic arrhythmia with extrasystoles arising in the same focus

While, as stated above in this chapter, we fully realize that our knowledge about this subject is very scanty, we believe that recent advances particularly in neurophysiology have thrown some light on this complex problem.

A few generations ago it may well have seemed heretical to base any concept of cardiac impulse formation on analogies with neuro-physiological data, at a time when the long controversy between the neurogenic and myogenic theories of the origin of the heart beat seemed, at last, to have been firmly decided in favour of the latter. Of late, however, the similarities rather than the differences in this respect between heart, nerve, ganglia and skeletal muscle have tended to be emphasized. The following quotations from a recent textbook of physiology are significant in this context. "An impulse arising in this part of heart, differing from an impulse passing over a nerve fiber only in the anatomical complexity of the pathways it follows and in the variations in rate of conduction associated with them." (Hoff, in Fulton, p. 596) "It will be seen that although the heart beat originates in muscle tissues, the essential physiological properties of pacemaking myocardial cells which make possible the rhythmic beat of the heart are little if any different from those of nerve fibers, nerve cells, sense organs, and even skeletal muscle fibers, which can and under the proper circumstances do act like the pacemaker to set up autogenic rhythms" (*Ibid.* p 599) Regarding the electrical changes in skeletal muscle "Qualitatively and in general outline the muscle action potentials are identical with those of a nerve . " "The mechanism of excitation, also, is generally held to be essentially the same for muscle and nerve membranes" (Gelfan, *ibid.* p. 116)

Such analogies will, we hope, become also apparent in the discussion which follows.

Some Relevant Physiological Data about Initiation and Propagation of Excitation

This emphasis on the similarity of processes underlying the activity, particularly the

a negative after-potential A phase of subnormal excitability may succeed which is accompanied by a positive after-potential. It is the supernormal phase of recovery with its associated negative after-potential which is of special interest in regard to extrasystoles.

The supernormal phase was first found in nerve by Adrian and Keith Lucas (1912) and described as a temporary overswing of the recovery curve of excitable tissue after the transmission of an impulse. During this phase—lasting in nerve about 0 015 second—stimuli of an intensity which at any other time would be subliminal become effective. Later, Adrian (1920) demonstrated the presence of a supernormal phase of recovery in the cardiac muscle of the frog in certain experimental conditions (for example, perfusion with a relatively acid fluid) Wastl found it in the fatigued preparation, and Eccles and Hoff encountered it occasionally in the pacemaker of decerebrate cats Ashman demonstrated it in the compressed heart of the turtle, but Lewis and Master were unable to establish it in the dog's heart More recently, Hoff and Nahum found it in the ventricle of fourteen cats anaesthetized with barbiturates, while in seven out of nine decerebrate animals it was absent. The supernormal phase coincided either with the terminal portion of the T wave, or with a U wave when present. It is, however, not proved that the U wave signifies an after-potential of the kind of the negative after-potential (Schaefer, 1942, p 16)

The number of observations indicating the presence of a supernormal phase in man is very small, and of the published cases several admit of alternative explanations of the arrhythmia But even the most critical review of the published cases (Mack, Langendorf and Katz, 1947) had to concede that in five cases a supernormal phase has to be considered present (Luten and Pope; Jervell, Scherf and Schott, 1939, two cases, Froment, Masson and Gonin, Case 1) and to these they added one of their own In others, while alternative explanations were preferred, the proposed alternatives are, in our opinion, no more probable than the assumption of a supernormal phase A more detailed discussion of the individual papers dealing with such observations in man would be outside the scope of this book The reader is referred to the quoted paper by Mack, Langendorf and Katz, but should bear in mind that the explanations favoured by these authors are, for some of the cases, based on an alternative mechanism suggested by Wolferth (1928) on the assumption that there was no proof that mammalian heart is capable of a supernormal phase; this view is no longer tenable. Nor does it seem justified to consider supernormality of excitability and that of conduction as separate phenomena, as is implied in the quoted paper, since the two go hand in hand (Segers 1941, *see also* below) In our opinion a supernormal phase of recovery may well play a greater rôle in clinical arrhythmias than was thought in the past

One of the earlier experimental studies in which the supernormal phase was considered as one of several factors to account for ectopic arrhythmias is the one by Ashman and Hafkesbring (1925) Using turtle hearts in which the sinus was ligated off, they found ectopic rhythms arising either spontaneously or as the result of one sub-liminal shock. The rate of such rhythms, resembling Luciani periods, first increased, then decreased. Ashman and Hafkesbring explained such arrhythmias on the ground of the following assumptions discharge of impulses from an ectopic centre on attainment of a sufficient degree of excitability, supernormal phase in the period of returning excitability; treppe in excitability for the first several recoveries of a period, fatigue of the ectopic focus resulting from its activity and recovery from fatigue during the quiescent periods. With increasing rates of electrical stimulation during intervals of spontaneous rhythm the ectopic rhythms occurred at successively later intervals and the groups of ectopic beats became successively shorter until with fast stimulation they became reduced to one single ectopic beat. These authors concluded that, if the ectopic focus in man was similar to that in the turtle heart, " it might, as permitted by conditions of nerve influences, sinus rhythm, and degree of supernormal recovery, discharge either single ectopic impulses, multiple ectopic impulses, or series of

impulses producing paroxysmal tachycardia ". They pointed out that such a focus should not be considered as an automatic blocked-off focus, " but as a potential pacemaker, normally responding to every sinus impulse until conditions favour its assumption of the rôle of actual pacemaker " They also emphasized that very gradual changes in the condition of the focus could lead to the sudden onset or end of a paroxysm It will be seen that much of the more recent work, particularly on nerve, accords well with this view and has brought to light some of the finer mechanism operating in such a focus.

Super-normal phase and negative after-potential are co-existing phenomena. When the latter is prolonged by fatigue or drugs (for example veratrine), the former is altered in the same way and both are shortened by cooling (Gasser and Erlanger, 1930) According to Gasser and Grundfest the association, in the mammalian nerve, between negative after-potential and super-normal excitability on the one hand, and between positive after-potential and sub-normal excitability on the other, is so close that " the curve of excitability should be as characteristic of the nerve and its various states as is the action-potential We shall see that the rule holds " These authors also found that a second, third and fourth negative potential may follow the first one, that the play between negative and positive after-potentials behaved like damped oscillations, and that preparations showing this phenomenon were also subject to spontaneous discharges which increased during the negative, *and decreased during the positive phases of after-potentials It was then shown by*

(1937b) to de-ionization of calcium, since exclusion of calcium or citrate had the same effect as increase in pH, namely lowering of threshold to electrical stimulation and occurrence of spontaneous discharges This explanation was contested by Lorente de No (1947) in whose opinion citrate and oxalate exert their effect by lowering the membrane potential He adduced several reasons why the effect of citrate is unlikely to be due to its immobilizing calcium and established that oxalate does in fact lower the membrane potential, namely the L fraction (Lorente de Nó and Feng)

In nerve poisoned with veratrine, however, a large and prolonged negative after-potential may occur in the complete absence of supernormality and some unknown factor, additional to the negative after-potential, seems to underlie supernormality (*see* Krayer and Acheson)

Erlanger and Gasser (1937) summarized some particulars about these phenomena of which the following may briefly be mentioned supernormality was not found in freshly isolated frog's nerve, but developed in the course of the experiment as the negative after-potential grew " The end of the relatively refractory period comes earlier, but excitability increases for the same length of time as before, and thus the maximum of excitability gets to be definitely greater than the excitability at rest. Supernormal excitability then continues during the progress of the negative after-potential, and at the same time conduction becomes supernormal in velocity " Furthermore, these authors point out that, in contradistinction to the constancy of the spike and of the absolute refractory period, the after-potentials are very variable Regarding the significance of supernormality, the following sentence *indicates its importance in the context of* this book " Raising the excitability temporarily, either from the resting level or an equilibrated subnormal level, supplies an excellent mechanism for picking up excitation from a subthreshold background." This they illustrate by the following example which also confirms a similar previous observation of Gasser and Grundfest a mammalian nerve is stimulated by thyratron shocks at a rate somewhat above 100 per second and at a strength just at threshold for the most irritable fibres If a single shock is added sufficiently strong to excite the whole nerve, the subsequent thyratron shocks, falling in the supernormal phase—at first of the strong induction shock,

subsequently of the preceding propagated disturbance—become supra-threshold and this phenomenon repeats itself until a gradually growing positive potential, associated with subnormality, terminates the response. This is a modern illustration of an observation of great importance for the understanding of extrasystoles, namely, the Wedensky effect.

The Wedensky Effect and Allied Observations

In 1886 Wedensky found in the sciatic-gastrocnemius preparation of frogs that subthreshold faradic stimulation of the nerve (which did, of course, not result in any contraction) was followed b ... mally to the site of ... s confirmed by sever ... s "Wedensky effect" is enhanced by hypertonic solutions of glucose or NaCl, by Ba··, Ca· and Mg··, reduced by hypotonic solutions of glucose or NaCl, by H·, Li·, OH' Rb and K Mogendowitsch subsequently established that the application of a moistened crystal of NaCl between the muscle and the site of stimulation (induction shocks) also precipitated the "Wedensky effect". He made the further important observation that it was immaterial whether the stimulating electrodes were applied proximally or distally of the site of application of the NaCl crystal He offers the following explanation A single excitation which has just arrived in an altered locus there produces a more or less lasting increase in excitability owing to which subthreshold impulses become suprathreshold. The single excitation wave can act either direct or by way of ricochet "In order for a summation of excitation of the type of a tetanus-like single twitch to occur it is not always necessary for the single excitation to pass through the altered locus. It is sufficient if it penetrates into the focus, irrespective of its position" (Our translation)* This observation illustrates one variety of conditions "for picking up excitation from a subthreshold background" (see above) and also the importance of chemical stimulation in the production of repetitive discharge, discussed below (p 507)

Samojloff established that, contrary to Wedensky's interpretation, the phenomenon actually is a true tetanus He also made the important observation that the "activating" effect of the single induction shock lasted through a considerable time It could be demonstrated if the sub-threshold stimulation was started as long as 0 2 second ...

ceed the duration of the supernormal phase and Samojloff puts forward the explanation that such shocks act through "Bahnung" (facilitation) at the myoneural junction. To a certain extent this explanation is supported by an observation of Denny-Brown and Sherrington on decerebrate cats stimulation of a sensory nerve (saphenus) at fifty per second resulted in a reflex tetanic contraction of the M tensor fasciae femoris If, in addition, another sensory nerve (musculocutaneous) was stimulated with a single shock, the existing tetanus ...

direct electrical stimulation upon the contraction and action currents of fully curarized skeletal muscle, and certain observations on paraesthesiae in man: if such sensation,

* Die Erregungssummation vom Typus der tetanisierten Einzelzuckung verlangt nicht durchaus ein Hindurchgehen des Einzelreizes durch die alterierte Strecke. Es genugt dazu das Eindringen in den Entstehungsherd, unabhangig von dessen Lage

elicited by a constant current, was disappearing and already very indistinct, one induction shock made the paraesthesiae flare up again for some time (Ebbecke). Similar observations were made by Schaefer and Schmitz . a constant current of a certain strength, applied to a cutaneous nerve, produced a sensation of warmth in the distribution of the nerve, if a mechanical stimulus was applied in addition, it caused a transient sensation of warmth (apart from the tactile sensation) which was quite different from the effect of the same mechanical stimulation of a neighbouring area These authors draw attention to the analogies between their observations and those of Wedensky, and of Denny-Brown and Sherrington, quoted above.

Goldenberg and Rothberger (1933) confirmed the presence of this " Wedensky effect " on excised Purkinje fibres of the dog, stimulated by means of condenser discharges. If the fibres responded to near-threshold shocks by contraction to only a certain fraction of the applied stimuli, single strong induction shocks lowered the threshold so that a 1 : 1 response ensued for a varying number of such juxta-threshold stimuli If sub-threshold condenser shocks were used, a single induction shock so lowered the threshold that long groups of 1 : 1 responses followed Spontaneous automatic beats had the same " activating " effect. Applying these findings to clinical ectopic arrhythmias, Goldenberg and Rothberger interpreted them as indicating the activity of an ectopic centre, located in a branch of the specialized conducting system, the impulses of which become effective only during a certain phase of increased excitability consequent upon the preceding beat.*

More recently, Harris and Rojas concluded that coupled beats observed in the dog's heart after coronary occlusion were best explained as resulting from recovery through supernormality The employment of multiple simultaneous electrograms made it possible to exclude the possibility of a circuitous conduction being responsible for such bigeminy. In experiments on cats, Hoff and Grant found that with an arterial pH of 7 2 there was no supernormal phase and no spontaneous ectopic beats occurred. When, by intravenous injection of 4 cc of n/20 HCl, the arterial pH was lowered to 7 1, series of ventricular ectopic beats occurred after stimulation and persisted after it was discontinued, short bursts of tachycardia and coupled beats were observed When, subsequently, the administration of acid was slowed and the coupled beats had disappeared, a supernormal period was found in that part of the cycle in which the coupled beats had occurred.

In a subsequent paper Goldenberg and Rothberger (1935) investigated the effect, upon such arrhythmias, of localized injury by compression, stretching or supra-maximal break shocks The result was an increase in rate, which the authors attributed to faster depolarization of the centre. That stretching increases the rate of depolarization markedly follows from more recent experiments of Scherf, Scharf and Goklen which demonstrated that stretching increased the rate of ectopic auricular arrhythmias elicited by the topical application of aconitine. If the effect of aconitine had subsided short paroxysms of the tachycardia could be made to reappear by stretching (*see* section on " Flutter and Fibrillation ") Fig. 212 illustrates a left ventricular tachycardia which occurred in a dog during an attempt at cutting the left bundle branch. That continuous stimuli may result in rhythmical discharges will be discussed below

The relationship between extrasystoles, after-potentials and—with some qualifications already referred to (p 499)—enhanced excitability follows even more clearly from experiments with veratrine, which is known to produce a marked prolongation of the negative after-potential In addition to causing prolongation of systole generally (which may increase from 0 1 to 60 seconds) and of contraction of Purkinje fibres, it produces various

* [illegible]

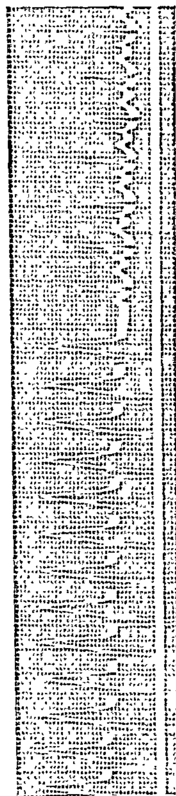


Fig 212 —From an experiment on a dog Left ventricular tachycardia occurring during an attempt at cutting the left bundle branch

arrhythmias in Purkinje fibres which were investigated by Wachstein and more extensively studied by Goldenberg and Rothberger (1936). The latter authors used mechanograms and electrograms Two kinds of arrhythmias were found interferences and "oscillations" The latter, following a large initial contraction, were shown by the electrogram to be due to rapid excitations superimposed upon an enormously prolonged after-potential They resembled tachycardic attacks, having a fixed coupling to the large initial beat and being followed by a pause, free from oscillations, which resembled a post-extrasystolic interval The authors concluded that such oscillations were due to otherwise sub-threshold impulses which became effective during the negative after-potential More recent work suggests as an alternative explanation that the increased negative after-potential is alone sufficient to give rise to spontaneous impulse formation This has been established in various structures, the end plate potential in the isolated nerve-muscle preparation of frogs may be quoted as one example (Eccles, Katz and Kuffler)

Other, allied, conditions which produce an increase in excitability and may have a bearing on the mechanism of origin of extrasystoles may briefly be mentioned.

One such instance is the increase in excitability beyond a nerve block, discovered also by Wedensky and commonly known as Wedensky facilitation Such a block can be induced in various ways, for example cold, drugs, or pressure. Wedensky (1903), who used various chemicals, found that the threshold of the segment below the block becomes lower than it was before If such a block has become complete, impulses will not be transmitted through the block zone, but as such impulses are stopped at the proximal margin of the block, the threshold, to electrical stimuli, of the nerve below the block is lowered, "the lowering of threshold being a cumulative and enduring process" (Lorente de Nó, 1939) Hodgkin (1937) has shown that this effect, upon the excitability of the zone below the block, of the stopped impulses is due to the spread of electrotonic current, producing an "extrinsic potential" beyond the block Lorente de Nó (1939) demonstrated, in addition, that residual negativity (resembling, but not necessarily identical with, true after-potentials) is also transmitted through a block It seems that such slower changes in residual negativity (spreading over a greater distance than those due to the faster spike-like potentials) are related to facilitation of transmission, without acting as transmitters themselves

Changes of Excitability and of Potential after Sub-threshold Stimulation

Such changes, being local ones and closely associated with the "local response", are more conveniently discussed in connexion with these phenomena (*see* below, p. 510).

The relevant points, in connexion with the mode of origin of extrasystoles, of these observations are·

A supernormal period of recovery, associated with a negative after-potential, has been found in various tissues, and while the extent of its importance in cardiac arrhythmias is still controversial, its presence in cardiac muscle has been established. During such period of enhanced excitability impulses, which at any other time are sub-threshold, become effective, or are formed. The after-potentials and associated changes of excitability are less constant, and more susceptible to environmental changes, than the propagated disturbances Such temporary increase in excitability after a conducted excitation must be assumed to [illegible] the time relations in repetitive responses to a single stimulus which have now to be discussed.

Repetitive Response to Continuous Stimuli

Introductory Remarks

The striking resemblance between phenomena observed in Lillie's iron wire model and those in living tissue has often been commented upon an iron wire placed in nitric acid of certain concentrations develops a passive state owing to the formation of a thin layer of oxide If such a wire is "stimulated" in one of several ways, that is, if the protective film is locally destroyed temporarily, local electrical currents originate which the wire transmits along its length and which can be recorded with a string galvanometer; subsequently the passive state of the wire is restored This process of transmission is due to the breakdown and subsequent re-forming of the oxide film In certain experimental conditions a *continuous* "stimulating" reaction in a localized region of the wire—for example contact of the metal with glass—also produces *rhythmical* electrical transmitted changes, the rate of which depends on the concentration of the acid, after each transmission there is a non-transmissive "refractory" period The analogies with conditions prevailing in the heart are obvious

Another chemical model, showing periodicity and rhythmicity, which has recently been studied in more detail from the point of view of analogies with biological rhythms, is the decomposition of H_2O_2 into H_2O and O_2 in the presence of metallic Hg acting as catalyst (Ernst)

The first observation in living tissue of a repetitive response to a constant stimulus was reported in 1859 by Pfluger who found in the nerve-muscle preparation of frogs that constant currents of certain intensities produced tetanus, whereas weaker or stronger currents failed to do so He explained this observation tentatively by the extent of the zones of increased and decreased excitability Pfluger's observation was confirmed by several authors (for refs *see* Schriever and Cebulla)

One year after Pfluger, Kuhne reported "wave-like excitations following one another at short distances if a thin muscle with parallel fibres is placed across the electrodes of a chain of galvanic batteries" (our translation) ("dicht gedrangte wellenartige Erregungen wenn man einen dunnen Muskel mit parallelen Fasern uber die Elektroden einer konstanten Kette legt") This phenomenon has recently been studied in some more detail by Klinghardt, including the effect of various ions and of veratrine Rhythmic contractions of

skeletal muscles due to continuous stimulation with faradic or alternating current were described by Fraenkel and by Neuroth (*see also* Bethe, 1926, 1952, in whose Institute this work was carried out)

The repetitive response to continuous stimuli has been studied in a great variety of circumstances (*see* for example Fessard, 1936, Lorente de Nó and Feng, 1946) Earlier in this chapter reference was made to the effect, on arrhythmias observed in Purkinje fibres, of continuous depolarization of a circumscribed area Altogether the rhythmic response to continuous stimuli is a widespread biological phenomenon· the response of the optic nerve to light, of sensory nerves to a great variety of continuous stimuli, to quote only two instances (*see* also Bethe, 1952).

Some other relevant observations have now to be discussed in some detail.

Injury

Adrian (1930) recorded, in nerves of cats and rabbits, the action potentials resulting from injury. He distinguished three main types of discharge (1) continuous and regular succession of impulses at a high frequency, rarely less than 150 per second, (2) an irregular succession at lower frequency, and (3) a grouped discharge, each group consisting of several impulses very closely spaced and the successive groups following one another at a very low frequency, namely ten per second or less. Adrian concluded that " the detailed arrangement of the continuous and grouped discharges is due to the periodicity imposed by the recovery process of the nerve fibre, and that the excitation remains relatively constant over periods which are long compared with the total recovery time of the fibre " Regarding the observed grouping of the impulses within the individual groups, this could be explained by assuming a steady excitation of gradually decreasing intensity, this decrease being due to some opposing change in the tissue *

Electrical Stimulation

The opposing change, as postulated by Adrian, was considered in more detail in the studies of B Katz (1936) on multiple response to constant current in frog's medullated nerve Katz based his study on Hill's theory of electric excitation by a constant current. According to this, the applied current rapidly builds up at the cathode a " local potential " V which is maintained throughout the passage of the current; excitation occurs if and when V becomes greater than the threshold U. This threshold rises at a rate determined at any moment by the value of V at that moment and by the time constant λ of " accommodation ", the opposing factor of Adrian During the interval at which V is greater than U, repetitive responses may be expected to occur at intervals determined by the refractory phase. *The length of the interval during which repetitive responses can be expected will be* greater the slower the accommodation, that is the greater the value of λ Katz found the results of experiments in accordance with theory· in nerves of cooled frogs repetitive response to constant current of slightly more than rheobasic strength was observed and in such conditions accommodation was found to be very slow, λ being at first 300 msec. and even after four to six hours' soaking at room temperature still being above 100 msec. On the other hand, interferences resulting in shortening the time of accommodation reduced or abolished repetitive response (for example, soaking the nerves in Ca-rich solution) The widely studied effect of the reduction or removal of Ca in inducing repetitive response and spontaneous activity was found by Katz to be associated with a great increase in the time constant λ of accommodation and a considerable lowering of threshold. These

* Injury potentials were considered to be one of several factors in the origin of ectopic beats after experimental coronary occlusion (Harris) and are held to account for ectopic arrhythmias which occur during cardiac catheterization

observations emphasize the importance of the ionic milieu and are related to investigations on chemical stimulation, discussed below.

According to Schriever and Cebulla the process termed "accommodation" is more complex, and it is the gradient of current necessary to excite, which varies in a characteristic fashion according to whether the response is non-rhythmic or rhythmic.

Erlanger and Blair's studies (1936) on repetitive responses in the phalangeal nerves of frogs bring out several features of importance in connexion with the mode of origin of extrasystoles. In these investigations *stimulation by means of rectangular currents* was used. While the usual response of the excised frog's nerve consists of a single action potential, repetitive responses were observed in a variety of conditions These authors point out that repetition induced by rectangular current is characterized by its unpredictability and that, if a fibre repeats, it does so only when the current is applied to more or less definite loci of the fibre. Repetition was found to be rapid (with rare exceptions) and was either immediate or delayed. Regarding the latter. "the interval between closing of the current and the beginning of the repetition is longer, it may be very much longer, than the sum of the utilization period and the conduction time involved". Delay as long as 0 2 second was observed "though no effort has been made to determine the limit" It is noteworthy that such figures are of the order of length of coupling of extrasystoles (Regarding the mechanism underlying such long periods, *see* below local response) Even if repetition gradually failed, the repetition pattern, as obtained from a fibre at a given point, usually remained constant —another analogy to extrasystoles. Anodal polarization was found to be of great impor-

somewhat the number of responses. It was also found that by anodal polarization the correlation between changes in excitability and repetition could be greatly improved, to such an extent that the authors came to the following conclusions ". . that fibers that have exhibited delayed repetition but which were not being subjected to artificial anodal polarization, either were anodally polarized, presumably by local demarcation currents, or else were subject to some other condition which produces a state similar to the anelectrotonic state".

These findings, namely, the importance of local demarcation currents or of a condition producing a similar effect, may well be applicable to the mode of origin of some instances of extrasystoles The importance of anodal polarization in the production of fibrillation of the dog's heart (Harris and Moe) is referred to in the section on fibrillation (p 231) Moreover, amongst the data which Erlanger and Blair discuss in connexion with the exact *site of origin of repetition is the observation of Schaefer and Schmitz that an action potential passing into an injured locus may initiate an after-discharge there. In nerve-muscle prepara*tions of frogs Schaefer and Schmitz investigated, by means of an oscillograph, the changes in the action currents which occurred if the excitation had to traverse a portion of nerve injured by compression The nerve was stimulated by induction shocks of threshold strength These authors found that the previously smooth curve of the action potential was, after injury, followed by a series of small oscillations at intervals of 0 5–1 msec, lasting 10–20 msec A similar phenomenon was observed if the excitation had to traverse a locus which was strongly polarized anodally here the action potential became strongly deformed in its descending portion and showed numerous waves, indicating that numerous action potentials had become superimposed on the otherwise uniform action potential "The arriving excitation precipitates new individual discharges Before the arrival of the

action potential the locus in question of the nerve was quiescent, as shown by the oscillogram" (our translation) *

While Erlanger and Blair reject this mechanism as explanation for their findings, it seems to us that it may well be of importance in the mode of origin of extrasystoles This opinion is based, *inter alia*, on the following observation by Arvanitaki (1937c): A small area *a* of a nerve fibre is anodally polarized or subjected to warming (that is, interferences lengthening the after-potentials). One of two recording electrodes is placed on *a*, the other at a distance at *b* The nerve is electrically stimulated beyond *b* with juxta-threshold currents In these circumstances an impulse coming from *b* and conducted to *a*—called "afferent impulse"—is followed by a large after-potential at *a* which there initiates a spike which is conducted from *a* to *b*, called "efferent" impulse. It was also found that the changes precipitated at *a* by the "afferent" impulse are an essentially graduated phenomenon which is capable of summation (*see* also below, local response). If the temperature at *a* was gradually raised, the after-potentials gradually increased and repetitive responses occurred. The same repetitive response could also be observed if the "afferent" impulse did not actually reach *a*, but was blocked in its neighbourhood These observations demonstrate the importance, *for precipitating an ectopic impulse, of* anodality (or allied *conditions regarding after-potentials) of the "ectopic centre" as well* as the fact that the initiating impulse need not actually reach the "ectopic centre".

Similar observations were made on strips of the heart of the tortoise by Segers (1940). Strips of 10 cm. length were suspended in two compartments A and B which were separated by a partition, a hole in which allowed the strip to be put through. Such preparations did not show spontaneous contractions. Addition in A of two or three drops of a 1-per-cent solution of adrenaline alone did not cause any activity, but after sufficiently long electrical stimulation of the end of the strip in A a series of about ten spontaneous contractions occurred which lasted beyond the end of stimulation If the strip was stimulated at its end B, the forced beat was propagated to A, but after the end of stimulation a series of spontaneous contractions occurred in A which were propagated towards B. Segers concluded. "Le battement rythmé spontané de l'extrémité A apparaît comme conséquence de l'activité provoquée à ce niveau par les ondes d'excitation physiologique provenant de l'extrémité B, celles-ci déterminent donc la même réaction consécutive que la stimulation électrique de *l'extremite A elle-même" With sufficient adrenaline added in A, one excitation elicited* in B precipitated a contraction wave travelling from B toward A, followed by a second wave in the reverse direction Similar effects were seen with $CaCl_2$ and $BaCl_2$ (applied in A), such repetitive or "reflected" contractions were suppressed by K or yohimbine. Segers attributed such after-reactions to the negative after-potential acting in the manner of a catelectrotonus

More recently Dawes and Vane studied repetitive discharges in the isolated auricle of guinea-pigs They stimulated the preparation by means of square constant current pulses at a rate slightly greater than the normal rate, every fourth stimulus was followed at a predetermined time interval by a test-pulse of similar form and duration, but variable strength. They found that if the test pulse, of adequate strength, fell just outside the absolute refractory period the auricle not uncommonly responded by repetitive discharges, varying in number between two and ten, and occurring at a frequency much greater than that of normal beats, up to 15 per second Spontaneous discharges sometimes continued for a long time, up to one hour *These authors assumed that such discharges originated from the neighbourhood* of the stimulating electrode and may be due to persistence of a supernormal period.

To revert to Erlanger and Blair's studies: amongst the conditions listed as "accessory to the initiation of induced repetition" is the rise in excitability responsible for the treppe

* "Die ankommende Erregung gibt den Anstoss zu neuen Einzelentladungen Vor Ankunft war die betreffende Nervenstelle, wie das Oszillogramm zeigte, in Ruhe" P. 168

phenomenon. Regarding this, the following observation is described: In one experiment a rectangular current, which was just below the repeater threshold, occasionally stimulated one or more axons on breaking. "Whenever a break response occurred, the next application of the constant current and several of the succeeding ones resulted in bursts of repetitions appearing when the rectangular current was closed, but some time after its make—with a long delay, in other words. We have good reasons for believing that in this preparation the increase in excitability resulting from a single response lasted through a second at least, and it is concluded, therefore, that the repetitive bursts occurring during the rectangular current developed in the treppe that was initiated by the response elicited by the break of the constant current." This observation seems to us of importance as being another illustration of a very long-lasting increase in excitability following one response.

Analysis of the intermissions in a repetitive response showed that they were not due to a block along the conducting path, but to oscillatory changes in the recovery curve, in particular "that the recovery period of a fiber is the first of a continuing series of oscillations in excitability with a period about equal to the recovery period" Such changes in excitability were actually found and Erlanger and Blair concluded that "the first low threshold point must be equivalent of, if it is not actually, the supernormal phase." The period of such (decrementing) oscillations, about 5 msec, was of the same order as the period of repetition of the fibre.

The findings of these extensive investigations which seem to us most relevant in connexion with the mode of origin of extrasystoles can be *summarized* thus The occurrence, in certain conditions, of repetitive responses to a stimulus which ordinarily results in only one action potential, the repetitive response being confined to certain loci of a nerve fibre or portions of a strip of cardiac muscle, the great importance of anodal polarization, or a condition producing a similar effect, and thus of local demarcation potentials and of changes in the ionic milieu in producing repetitive response; the possibility of an action potential's passing into an injured or chemically altered locus, there setting up new rhythmic action potentials, the long delay in the onset of repetition after the precipitating stimulus, greatly exceeding utilization time + conduction time (corresponding to coupling); the observation of a very long-lasting increase in excitability after a single break response, the importance of oscillatory changes in excitability during recovery

Chemical Stimulation

The work considered so far was concerned with rhythmic activities precipitated by injury or by constant current (or single induction shocks or current pulses) Chemical stimulation provides another mechanism of a constant stimulus and the rhythmic activities resulting from this kind of stimulation have been extensively studied (for references on early work see Mines, 1908) Several references to the topical application, to the epicardium or the sub-epicardial layers, of various chemical compounds will be found in this chapter as well as in the appropriate sections of the chapter on drugs (sodium, barium, digitalis) The importance of the ionic milieu in connexion with excitability to electric stimulation has been repeatedly mentioned earlier in this chapter In addition, a few investigations warrant a more detailed discussion in the present context.

In nerves the application of crystals of calcium chloride or any salt producing a high osmotic pressure precipitated a high frequency discharge (Adrian, 1932)

In the nerve of the crab, where repetition is easily observed generally, it could be induced by a variety of chemicals (Auger and Fessard, 1933). Rhythmic discharges were not noted in fresh nerves, but by keeping them in sea-water for one to two hours this property could easily be elicited (Arvanitaki and Fessard, 1934). Besides various inorganic compounds, amongst which Na hyposulfite proved particularly efficacious, excess of OH′ (pH about 11) and various alcohols were found effective in this respect (Fessard, 1936) The slow

variations of the base line, which was found in such experiments in addition to rhythmic discharges, will be discussed below in connexion with "pre-potentials".

In numerous investigations partial removal of Ca·· has been found to favour the occurrence of rhythmic discharges. Brink and Bronk (1937) investigated this in the sciatic nerve of frogs. By citrate, or by reduction in concentration, partial removal of Ca was effected at one portion, usually one end of the nerve. In such conditions continuous trains of impulses of a frequency of about 100 per sec. were observed to originate in the treated region If Ringer's solution was then substituted, the continuous train of impulses was transformed into series of rhythmic volleys, that is bursts of impulses following in succession The duration of such volleys then declined and after a period of transition a fairly constant state ensued during which the duration of the volleys may amount to several seconds, or each volley may continue for one or two minutes and recur every ten minutes. "But even at these longer intervals the volleys and the periods of silence are constant to within a few per cent. for an hour or more." The authors point out certain similarities between these observations and those made in connexion with injury (Adrian, 1930, discussed above in this chapter) and alcohol-treated crustacean fibres (Fessard, 1936). While we fully appreciate the caution necessary to apply such observations to cardiac arrhythmias, we believe that they have a bearing on the mode of origin of extrasystoles in the following respect. rhythmic discharges following a continuous stimulus, and constancy of volleys and of periods of silence even with longer intervals are features comparable to the constancy of shape and of coupling of extrasystoles which, also, may be precipitated by some continuous stimulus and may, and often do, occur at long intervals

In view of the extensive use which has been made of barium salts in the investigations of cardiac arrhythmias Lorente de Nó and Feng's "Analysis of the effect of barium upon nerve with particular reference to rhythmic activity" (1946) is of special interest. Mention was made earlier in this chapter of Lorente de Nó's working hypothesis that the membrane potential can be imagined to consist of a Q (quick) fraction, related to the fast electrotonus and initiation of propagated spike potential, and a L (labile) fraction related to the after-potentials and excitability. Regarding barium-treated nerves Lorente de Nó and Feng point out that, in such nerves, the L fraction has a high value and, since lowering of this fraction is a necessary condition for spontaneous firing of impulses to occur, such spontaneous impulse formation does not regularly take place This, however, can readily be initiated b [illegible]
mation [illegible]
sharply di [illegible]
the slow component of the catelectrotonus, *i e.* the decrease of the L fraction of the membrane potential, reached a certain level" (p 448) During the flow of the applied current the rhythmic firing passed through a maximum and then decreased to a lower intensity; this is attributed to the fact that the catelectrotonus during the flow of current passes through a maximum and then decreases, but does not become low enough to allow a sufficiently high level of the L fraction of the membrane potential to be restored for the firing to be abolished. If, however, the nerve is kept in an atmosphere containing 5 per cent CO_2, the decrease of the catelectrotonus is usually sufficient to prevent rhythmic activity altogether during the further flow of current, this being due to the property of CO_2 to increase the L fraction of the membrane potential [illegible]
tions of Scherf (1930b) that, in dogs, inhal [illegible]
abolished extrasystoles elicited by aconitir [illegible],
the same gas mixture abolished ventricular ectopic tachycardias precipitated by barium (*see also* sections on aconitine and on barium).

Regarding the effect of conduction of impulses on the rhythmic firing during the negative after-potential, Lorente de Nó and Feng point out that this is analogous to a Pflüger's

tetanus. The phenomenon was studied in nerves maintained in an atmosphere of 5 per cent. CO_2 and 95 per cent. O_2 in which, owing to the presence of CO_2, the rhythmic after-discharge after a conducted impulse was short In these experimental conditions the repetitive firing after conduction of one volley was hardly detectable, increased with the number of volleys in the train, attaining a maximum with trains of 5–10 volleys and then decreasing with increasing length of tetanus, to disappear altogether with trains having more than 25 volleys. This is correlated with the behaviour of the negative after-potential observed with the various numbers of volleys: it reached a maximum with trains of 9 volleys, but with increasing length of trains above this " the rate of recovery of the membrane potential during the descending leg of the spike underwent a progressive increase during the tetanus" (p. 454)

There is thus an interesting similarity between these neurophysiological findings about the behaviour of barium-treated nerves and observations made upon ectopic arrhythmias produced in various ways by barium in mammalian hearts In the instance of barium, the beginning of the cardiological observations—1911— preceded the neurophysiological ones by several decades, whereas in many other respects neurophysiological work on impulse initiation and conduction is now far ahead of cardiological counterparts. These analogies also demonstrate that, within limits, the application to cardiophysiological phenomena of corresponding observations made on nerves is justified

Another property of barium salts deserves brief mention In addition to producing repetitive firing of impulses, they give rise to conduction block in certain experimental conditions (*see also* Feng) and of a peculiar type This association, also found with acetylcholine, may be of importance to account for the protective mechanism of ectopic centres (*see* p 331)

The extensive studies of Brink, Bronk and Larrabee (1946) are of importance in the present context especially from four points of view, namely, regarding the relationship between repetitive discharges and (1) excitability, (2) O_2 consumption, (3) potential gradient, and (4) local oscillatory changes of potential

These investigations were carried out on nerves of squids and frogs and were concerned mainly with the effect of Ca, K and acetyl-choline as chemical stimuli.

If the concentration of Ca was lowered below a certain level (0 3 mM in frog, 10 mM in squid nerves), self-initiated trains of propagated impulses started, that is, the axons transformed " the continuous action of a physical or chemical agent into a series of recurring events which are made manifest as nerve impulses " The frequency of impulses depended on the degree of lowering Ca and repetitive activity began after the rheobase had decreased to below 5 per cent of its initial value Such impulses usually began at random intervals and then increased in frequency, but sometimes they started with a high initial frequency and then declined to a lower level, the latter occurred usually after a previous period of chemical excitation that had been arrested by restoration of Ca, or during the actual restoration The former is somehow reminiscent of extrasystoles which so often precede paroxysmal tachycardia originating from the same focus, though the analogy breaks down in [illegible] rare exceptions, the rate of the tachycardia does not increase The latter observation [illegible] be likened to the clinical arrhythmia of " Extrasystolie a paroxysmes tachycardiques [illegible] it is assumed that, during the decline in frequency of the ectopic rhythm, the [illegible] takes over for a few beats

The effect of calcium removal seems complex, thus these authors showed [illegible] makes a nerve more sensitive to other ions, for instance KCl or tetra-[illegible] chloride

In studying conditions in pre- and postganglionic fibres these authors [illegible] response in the synaptic region also could be modified by varying the conc[illegible] When pre-ganglionic fibres were stimulated by repetitive electric shocks [illegible]

the cells discharged repetitively, but at a much lower frequency which, *inter alia*, depended on the characteristics of each cell. The question poses itself whether, or to what extent, conditions of synaptic transmission may be applicable to the mechanism of origin of extrasystoles

It was further found that increased rate of oxidation is essential for the initiation of impulses If an oxidation-inhibiting agent (sod azide) was applied to the citrate-treated portion of the nerve, a concentration of azide sufficient to restore oxidation to a normal rate was sufficient to suppress chemical excitation, but the Ca-deficient and azide-treated regions of nerve still conducted impulses produced by electrical stimuli This higher requirement of O_2 for the initiation of impulses, as compared with that for their conduction, may well have a bearing on the difference in mechanism between automatic and extrasystolic impulse formation The parallelism between O_2 consumption and spontaneous activity was, however, not present in all experimental circumstances investigated by Brink, Bronk and Larrabee.

The effect, upon impulse formation, of potential gradients applied at the site of Ca removal was investigated by these authors by creating such a potential gradient either chemically, or by applying it externally. Both methods gave the same results If, by increasing KCl in the solution of Na citrate, the Ca-deficient area was made electronegative to adjacent parts, the propagated nerve impulses occurred with reduced frequency, conversely, if the region was made electropositive to adjacent ones (by sodium thiocyanate), the frequency increased Similarly, if the direction of the externally applied current was such that it entered the citrate-treated region, the average frequency of impulses was reduced for a brief period; when the polarizing current was terminated, a transient increase in frequency was observed With reversal of the direction of the applied current the opposite changes in the frequency of impulses were observed These observations illustrate the great importance of a combination of chemical factors and potential gradients in initiating trains of impulses and in modifying their frequency. The existence of local potential gradients in the heart has to be assumed in certain circumstances, for instance injury potentials, the importance of the ionic environment in connexion with impulse formation in the heart has been assumed for a long time The above observations, in addition to showing that such assumptions have foundation in fact, reveal the mechanism of such factors in some detail.

Another observation of Brink, Bronk and Larrabee has a considerable bearing on the mode of origin of extrasystoles. In giant squid nerves deprived of Ca they found a local oscillatory response, of the same frequency as that of propagated impulses which they precede, but spikes were discharged only if the local oscillations were of sufficient magnitude. If the frequency of the propagated impulses varied, it was found that they often did so at rates of simple multiples. It could be demonstrated that such longer intervals were due to failure of conducted impulses to be initiated and not due to disturbances of conduction This finding may well have a bearing on the mechanism of exit block (in parasystole, see chapter on " Pararrhythmias ") The similarity of this observation with one of Erlanger and Blair's, discussed above, will be noted Such local oscillatory changes of potential have been extensively studied in recent years, their importance warrants a more detailed discussion

Local Changes of Potential (" Pre-potentials ") and Local Response

The discussion so far was concerned with conditions resulting in enhanced excitability after a propagated impulse, for example the supernormal phase of recovery, and those generally conducive to repetitive response to a single or continuous stimulus Another aspect remains to be considered, namely, the local processes at the site of impulse formation in their relation to the origin of propagated disturbances and to repetitive responses

The relationship between changes in excitability and those of potentials is discussed earlier in this chapter, and the close association between negative (after-) potentials and increase in excitability after a propagated impulse was emphasized. Similar relations hold good for sub-threshold stimuli A momentary increase in local excitability resulting from brief sub-threshold shocks was found in 1908 by Gildemeister. Bishop confirmed this for sub-threshold stimulation with galvanic currents. Erlanger and Blair (1931a, b) studied in more detail such changes in excitability, due to sub-threshold constant current as well as to sub-threshold induction shocks The relevant points of their results were that, during flow of a subrheobasic current directed cathodally with respect to the studied portion of the nerve, the excitability at first rises, attains a maximum and then falls to a lower, but still supernormal level Following the break of the cathodal current the excitability falls from above to below normal. The results after a sub-threshold induction shock were qualitatively the same. Gilson and Peugnet found the behaviour of heart muscle (strips of the ventricle of turtles' heart) qualitatively very similar to that of nerve, as found by Erlanger and Blair, but the time relations, as found in frog nerve at 25° C, had to be multiplied by about forty for the turtle ventricle Some local, also called secondary, process was assumed to account for these observations, also for the latency to electrical stimulation. The study of Rushton (1932) about the excitability of frog's nerve at various instants after the start of a constant current indicated an active local non-propagating process at the site of stimulation, being additional to the passive electric effect of the stimulus which it activates to produce a propagated spike (*see* also Arvanitaki, 1936, and Newton) These local responses have an electrical sign, namely, slow potential changes (for a comprehensive description, *see* Arvanitaki, 1938)

Such slow potential changes preceding the discharge of propagated impulses were found by Adrian (1931) in the ganglia of the water beetle (*Dytiscus marginalis*), and by Adrian and Gelfan (1933) in the sartorius muscle of the frog In the latter, the electric changes were recorded at the point of origin of discharges which were elicited by the strictly local application, at the site of the exploring electrode, of Na citrate, tartrate or oxalate. It was found that a slow wave of negativity preceding the discharge of the impulse was "almost invariable" and that, at times, oscillatory waves of the same order were also observed after the end of a discharge. A sustained negative potential associated with repetitive fibre discharges was found in some cardiomers of the ganglionated median cardiac nerve of *Limulus polyphemus* by Heinbecker, who localized the origin of this phenomenon in the large unipolar ganglion cells and drew attention to the correspondence of his observations with those of Adrian on the water beetle

In extensive investigations Arvanitaki came to the conclusion that a stimulating (supra-rheobasic rectangular) current precipitated the propagated discharge not only passively, but that an active local process, preceding the spike, was set up in addition In crustacean nerves, in which rhythmic activity was induced by OH' or ethyl alcohol, slow negative potentials were recorded which preceded grouped discharges (Arvanitaki and Fessard, 1934) The presence of such a process could also be deduced from a study of the latent intervals with currents of different strength and duration The conclusion was that the mechanism, by which stimulation was effective, consisted of two parts, namely, one passively conditioned by the current (passive polarization) and another, active one, which could continue in the absence of continuing polarization (Arvanitaki, 1937a, b) The main characteristics of such local changes of potential were found to be: they are graduated, continuous, of varying speed and while, as distinct from the spike, they are not propagated, they spread along the nerve, but with a considerable decrement and are no longer traceable at a distance of 3–5 mm (Arvanitaki, 1938, p. 27) In this they resemble the spread of electrotonus. All these local slow potentials, whether occurring spontaneously or induced, were found to have negative and positive components and "c'est à la variabilité de la résultante

reverse conditions obtain the local response is large, can be produced by shocks which are too weak to elicit any response in normal nerve, and turns into a propagated spike at a potential which is lower than that in normal nerve. These conditions are illustrated in Fig. 213, taken from Hodgkin's paper It seems to us that these findings have a bearing on the mode of origin of extrasystoles, for they reveal some of the finer mechanism which may underlie the occurrence of extrasystoles during the supernormal phase of the preceding beat. The same holds good for Hodgkin's observations regarding the local response during the refractory period. he points out that, whereas in a normal resting nerve the response decrements rapidly, in the refractory period this tendency is counteracted by the fact that the response is continually working itself into more excitable nerve. If the local response encountered suddenly a patch of nerve where the recovery was much more advanced than elsewhere, the activity would immediately start to spread faster, and the potential would rise

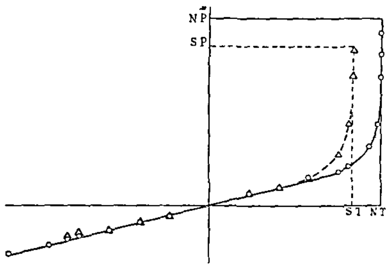


FIG 213 —Broker [illegible]
period Cont [illegible]
strength of s[illegible]
shock N T [illegible]
S P indicate [illegible]
supernorr[illegible]

steeply in the whole of the cathodic region " If the rise in potential were large enough, the response would be able to sustain itself by re-stimulation and would ultimately propagate throughout the fibre." " This experiment shows very clearly that there is no fundamental difference between a wave of activity which just succeeds in propagating and one which just fails."

If, in connexion with extrasystoles, a spontaneous impulse formation in the shape of a local change of potential at the site of the ectopic centre is substituted for the artificial subliminal stimulus of Hodgkin's experiments, similar conditions may well obtain in cardiac muscle. For in view of the constancy in shape and coupling of extrasystoles in the individual case the origin of extrasystoles of the common variety in one circumscribed and constant focus has to be assumed, and the presence of islets of temporarily refractory tissue near such focus has often been postulated in connexion with this and other varieties of cardiac arrhythmias.

In a more recent study Hodgkin (1948) investigated the local response associated with

repetitive discharges in isolated axons of crustacean nerve (*Carcinus maenas*). Such preparations could be divided into three main groups: (1) axons with a recovery cycle showing no significant supernormal phase; capable of repetition over a wide range of frequencies (5–150 per second); (2) axons with pronounced supernormal phase; this group usually produced trains of impulses of 75–150 per second " and was relatively insensitive to changes of the applied current "; and (3) axons with high threshold which either failed to repeat or did so only if the strength of the stimulating current was much greater than rheobase. Only the first two groups will be considered.

In axons belonging to group (1) it was found that the local response to sub-threshold currents was small as compared with the propagated spike potential, for example, in one experiment was 6 2 mV whereas the spike potential was 57 mV. The response time, that is the interval between the beginning of the stimulus and the first spike, was very long when the current was weak, measuring up to 0 098 second, and was of the same order as the intervals between successive impulses in the repetitive train "This observation suggests that response time rather than refractory period is the primary factor in determining the frequency of repetition when the current is weak." That the repetition frequency was very much smaller than could be accounted for by the refractory phase was observed also with stronger stimulating currents. with 5 per cent. above rheobase the repetitive responses would have had a frequency of 240 per second if the refractory period had been the sole determining factor, whereas the actual rate of repetition was about thirteen per second The refractory period became of importance with strong currents which tended to reduce the response time toward zero, but the repetition interval never became less than 6 5 msec Long response time makes, not only for a low rate of repetition, but also for stable low frequency discharges and it could be shown, in confirmation of previous work of Hodgkin and Rushton, that a long response time is associated with a prolonged local response Its growth can be very slow indeed, in extreme cases taking up to 950 msec. This local response is superimposed upon the passive depolarization and a spike potential originates when the depolarization reaches a certain critical level The whole process must repeat before a second spike of a repetitive response occurs, and a marked resemblance could be shown between the changes in potential which preceded the first impulse and those preceding "any other impulse in the repetitive train". Such changes need not be identical, because the rate of growth of the local response is exceedingly sensitive to small changes in current strength or excitability, and a very slight residue of supernormality or refractoriness may modify it.

In axons of group (2), that is those showing a pronounced supernormal phase, the frequency of repetitive discharge was comparatively insensitive to changes in the applied current Although supernormality is of importance in accounting for this, in this group of axons again this is not the sole factor determining the frequency For instance, the repetition rate was 90 per second at rheobase and 150 per second at 2 41 rheobase whereas, if supernormality were the sole determining factor, it would have been 540 per second Hodgkin explains *this by the assumption that, during the period of supernormality, the local* response develops at an increased rate and that, therefore, the spike arises earlier than it would do in the absence of a supernormal phase. But this does not mean that the spike must arise at the height of supernormality, it need not originate until after the end of the supernormal period This view is supported by the observation that the development of the local response was much faster during a supernormal phase than it was after the make of the current This accords well with Hodgkin's previous findings regarding the behaviour of the local response and its turning into a propagated spike potential during supernormality (*see* above)

In certain circumstances " the rate of growth of the local response may be exceedingly slow and both response time and repetition interval have exceeded 500 msec. on certain occasions ".

Of the results of these studies, those most relevant to the origin of extrasystoles, and of ectopic beats generally, may be *summarized* thus:

Local changes in potential, resulting from metabolic changes, apparently being a prerequisite for the discharge of propagated impulses; influence, upon such local changes of potential, of the supernormal phase of a preceding spike; independence of response time—corresponding to coupling—from the supernormal phase in the sense that the repetitive responses need not arise at the crest of supernormality and that response time as well as repetition interval may be very much longer than the interval during which supernormality can be assumed to exist; influence of the ionic environment on the number of repetition and on the setting up of automatic activity at the site of former stimulation, the effect, upon the local response, of refractory tissue with the result that the particular conditions may lead, either to a dying out of the local response, or to its growth into another propagated spike; the observation that small fluctuations in the strength of a near-threshold stimulus may produce very great differences in the local response and excitability, with the result that no fundamental difference seems to exist between a wave of activity which just succeeds in propagating and one which just fails; the possibility that a higher rate in O_2 consumption is necessary for automatic impulse formation in a centre than is necessary for the conduction of an impulse

MECHANISM OF ORIGIN OF ECTOPIC BEATS

If it is attempted to put forward some views about the mode of origin of ectopic beats on the grounds of the work discussed in this chapter, it must be stated at the outset that such views can only be tentative. Findings obtained in animal experiments can be applied [illegible] some ideas which, based on more recent advances in physiological knowledge and not conflicting with any known facts, provide some satisfactory, even if only partial, understanding of the experimental and clinical observations.

For all ectopic beats activity in a circumscribed centre has to be assumed.

Extrasystoles

To consider the common variety of extrasystoles with accurate coupling and constant shape first· here, the activity has to be located in one single circumscribed focus. In those numerous instances in which occasional extrasystoles are observed, separated by long periods of an undisturbed dominant rhythm, the activity in the ectopic centre must be sub-threshold for long periods. It seems reasonable to assume that it consists of some metabolic change, a fluctuation in resting metabolism which, as discussed above, has also been assumed to underlie the electrical sign of such local processes, namely, the local graduated, non-propagated changes in potential. Evidence has been discussed which tends [illegible] or in oscilla- [illegible] Such activity [illegible] lity and then manifests itself by producing a propagated impulse.

In order to explain the constant coupling of the extrasystoles the possible importance of the supernormal period of recovery comes first to mind. During this phase such subthreshold stimuli of the ectopic centre would temporarily become supra-threshold. Regarding the underlying mechanism, it was shown that, during the supernormal phase, the local response to a stimulus of a given strength is larger, and turns into a propagated impulse at a lower potential, than outside the supernormal period. Moreover, the propagated impulse

need not arise at the crest of supernormality, so that a strict coincidence between coupling and height of super-normality need not be postulated. Evidence, based on the effect of refractory tissue on the local response, was also cited which explains that not every beat of the dominant rhythm need be followed by an extrasystole. Whether an extrasystole follows each beat of the dominant rhythm or occurs only after a shorter or longer period of undisturbed dominant rhythm is, of course, only a matter of degree and is likely to depend on quantitative differences in the processes at the centre The inhibiting effect, upon the local response, of a propagated disturbance, and the possible presence of a period of subnormal excitability following the supernormal phase would seem to explain the observation that usually only one extrasystole occurs after the initiating beat.

The supernormal period is, however, not the only factor accounting for the occurrence and timing of the extrasystoles It was repeatedly mentioned earlier in this chapter that the activating effect of a propagated impulse could be noted for intervals which were far in excess of the supernormal phase For such instances Hodgkin's observations that the response time, rather than the refractory period or the supernormal phase, determine the frequency of repetition, and that the growth of the local response may be exceedingly slow

mality was discussed above

As far as the processes are concerned which produce the " subthreshold background "—to borrow a term employed by Erlanger and Gasser (1937)—most of this is still unknown. The local changes in potential, " pre-potentials ", found in various organs to precede the emission of propagated impulses were discussed earlier in this chapter It seems significant that, when these were oscillatory in character, their damping was found to be smallest in parts of the heart with the greatest automaticity, and greatest in those portions which have the least tendency to discharge spontaneously (Bozler) It was also mentioned that various investigators attribute such pre-potentials to fluctuations of metabolism, a view which is perhaps supported by observations on the relationship between initiation of impulses and O_2 consumption (p. 510) Beyond this, our ideas are only conjectural In particular, it seems obscure whether the underlying stimulus itself is continuous or rhythmical.

A wealth of evidence is available to show that continuous stimuli of various kinds and in various circumstances can initiate rhythmical responses If this be the case regarding the ectopic stimulus, injury potentials would first come to mind While these seem to be of importance in ectopic beats occurring immediately after myocardial infarction, in trauma, during cardiac catheterization, and possibly certain infections (diphtheria), such explanation is obviously inapplicable to those cases in which occasional extrasystoles with accurate coupling and constant shape are observed over periods of years Since a strictly circum-

akin to anodality, *or* may be related to the increase in excitability beyond a block, that is allied to, or identical with, the Wedensky facilitation

In the former case local circulatory changes resulting in changes in the ionic milieu would have to be considered in the first instance. In the latter case the local abnormality

each conducted beat

Whether or not a beat initiates an extrasystole in such a focus would depend on the

Of the results of these studies, those most relevant to the origin of extrasystoles, and of ectopic beats generally, may be *summarized* thus.

Local changes in potential, resulting from metabolic changes, apparently being a prerequisite for the discharge of propagated impulses, influence, upon such local changes of potential, of the supernormal phase of a preceding spike, independence of response time—corresponding to coupling—from the supernormal phase in the sense that the repetitive responses need not arise at the crest of supernormality and that response time as well as repetition interval may be very much longer than the interval during which supernormality can be assumed to exist; influence of the ionic environment on the number of repetition and on the setting up of automatic activity at the site of former stimulation; the effect, upon the local response, of refractory tissue with the result that the particular conditions may lead, either to a dying out of the local response, or to its growth into another propagated spike; the observation that small fluctuations in the strength of a near-threshold stimulus may produce very great differences in the local response and excitability, with the result that no fundamental difference seems to exist between a wave of activity which just succeeds in propagating and one which just fails, the possibility that a higher rate in O_2 consumption is necessary for automatic impulse formation in a centre than is necessary for the conduction of an impulse.

MECHANISM OF ORIGIN OF ECTOPIC BEATS

If it is attempted to put forward some views about the mode of origin of ectopic beats on the grounds of the work discussed in this chapter, it must be stated at the outset that such views can only be tentative Findings obtained in animal experiments can be applied to human pathology only with great reserve Moreover, however great the analogies found between the various excitable tissues, here again the greatest caution is necessary in applying findings obtained in one excitable tissue to others All that can be hoped for is to formulate some ideas which, based on more recent advances in physiological knowledge and not conflicting with any known facts, provide some satisfactory, even if only partial, understanding of the experimental and clinical observations

For all ectopic beats activity in a circumscribed centre has to be assumed.

Extrasystoles

To consider the common variety of extrasystoles with accurate coupling and constant shape first here, the activity has to be located in one single circumscribed focus. In those numerous instances in which occasional extrasystoles are observed, separated by long periods of an undisturbed dominant rhythm, the activity in the ectopic centre must be sub-threshold for long periods It seems reasonable to assume that it consists of some metabolic change, a fluctuation in resting metabolism which, as discussed above, has also been assumed to underlie the electrical sign of such local processes, namely, the local graduated, non-propagated changes in potential. Evidence has been discussed which tends to show that such changes consist, either in a gradually increasing negativity, or in oscillations, and that increased negativity is associated with increase in excitability. Such activity becomes supra-threshold if it exceeds a certain degree for a given excitability and then manifests itself by producing a propagated impulse.

In order to explain the constant coupling of the extrasystoles the possible importance of the supernormal period of recovery comes first to mind. During this phase such subthreshold stimuli of the ectopic centre would temporarily become supra-threshold. Regarding the underlying mechanism, it was shown that, during the supernormal phase, the local response to a stimulus of a given strength is larger, and turns into a propagated impulse at a lower potential, than outside the supernormal period. Moreover, the propagated impulse

neuromuscular block may be effected: the end-plate becomes less sensitive to the depolarizing action of acetylcholine, or too much acetyl-choline is released so that depolarization spreads beyond the end-plate region, or insufficient amounts of acetyl-choline are released by the nerve impulse" (Feldberg). Any of those conditions might produce a protective "block". It would seem a reasonable, though admittedly entirely hypothetical assumption to attribute such a protective blocking mechanism to acetylcholine which is known, on the one hand, to produce block in certain circumstances (for instance, decamethonium block, Burns, Paton and Vianna Dias; ganglionic block, Paton and Perry) and, on the other, to initiate ectopic impulses in the heart (discussed in the section on "Choline," p. 328)

Another possibility would be that the conducted S-A impulses fail to release a sufficient quantity of acetylcholine at the ectopic centre and thereby the centre is "blocked" Various conditions are known to produce this effect, amongst them calcium deficiency (Brown and Harvey) or perfusion with solutions rich in phosphate (Brown and Vianna Dias). Calcium deficiency is also known to favour automatic impulse formation, and in sympathetic ganglia some relationship seems to exist between acetylcholine deficiency, failure of transmission of excitation, and spontaneous activity in the form of repetitive discharge, in the causation of which calcium deficiency appears to play a part (Bronk *et al*, 1938, Harvey and McIntosh, see also section on "Choline") Burn's suggestion (Burn 1950) may be recalled once more in the present context that in cardiac muscle "the mechanism for firing off the contraction is also acetylcholine, but instead of being liberated by a nervous impulse it is synthetized and causes a contraction probably when a certain concentration is reached. It is possible that the pacemaker controls the rate of beating by controlling the rate at which this concentration is reached". If it is applicable to ectopic impulse formation it emphasizes the importance of acetylcholine and thus also the conditions which influence its effectiveness. That acetylcholine may play a greater part in the conduction of the cardiac impulse than hitherto assumed has been considered by Rothschuh as a result of his findings that the (frog) heart consists electrophysiologically of very small units, of the order of 0 1–0 2 m m, whereby in the mammalian heart the intercalated discs possibly form the anatomical basis.

Since metabolic changes generally are held to underlie impulse formation, an explanation along these lines suggests itself

The postulated biochemical disorder in or near the centre would be reminiscent of a similarly localized disorder in myasthenia gravis, though this comparison should by no means be taken to imply that identical conditions are assumed

Such a mechanism would also explain, at least to a certain extent, why automatic impulses do not become manifest during the supernormal phase of beats originating in other centres the altered condition of, or near the parasystolic centre, namely its reduced excitability as postulated to account for its protection, would equally prevent its sub-threshold potential changes from becoming supra-threshold during the supernormal phase of other beats Only when the automatic impulse has reached a certain intensity in the centre would a propagated disturbance ensue. We assume, therefore, that in parasystole the activity of the ectopic centre is more rhythmical than in extrasystoles, and sub-threshold processes play a much smaller, if any, part The mechanism of parasystolic impulse formation would thus be more akin to the normal impulse formation in the S-A node

In instances of parasystole with a fast ectopic rhythm the refractoriness produced by the fast ectopic rhythm accounts for the protection of the centre and no further mechanism need be assumed (see chapter on "Pararrhythmias")

Relationship between Extrasystolic and Automatic Beats arising in the same Centre

To take these relations in the same order as mentioned above (p. 495).

Automatic beats originating in the same focus as extrasystoles Here, the extrasystoles

have to be assumed to originate in the way discussed earlier in this chapter. In addition, there is a periodic protection of the centre, caused by the extrasystole in a way unknown, which makes possible the undisturbed formation of an impulse in the same centre. In addition to the extrasystoles, automatic beats are emitted whenever the local potential changes have reached the critical level at which they turn into propagated disturbances. This view accords well with some experimental findings on impulse formation in nerve (for instance Arvanitaki, Lehmann) and heart muscle (Segers).

Automatic beats followed by extrasystoles originating in the same centre could be understood as an arrhythmia in which the extrasystoles arise, in the supernormal phase of the initiating beat, in the same centre and in the same way as they are assumed to do after a precipitating beat of the dominant rhythm.

The transition from parasystole into an extrasystolic arrhythmia, which has been observed on rare occasions, is more difficult to explain on the grounds of the observations so far available It could be understood as resulting from the disappearance of those conditions which were discussed as accounting for a protective " block " of the ectopic centre. Such conditions were assumed to be functional ones, most probably metabolic in nature. (Their functional character would also account for observations of intermittent parasystole, and of the disappearance of parasystole after some time which we have not infrequently observed) If, owing to metabolic fluctuations, the biochemical disorder responsible for the protection of the ectopic focus is no longer present, this will be depolarized by the impulses of the dominant centre. A condition results in which the sub-threshold activities at the centre become supra-threshold during the supernormal phase of the preceding beat, that is, the centre produces extrasystoles with fixed coupling.

In conclusion, we should like to emphasize once more that the views on the mechanism underlying extrasystolic and automatic impulse formation should only be regarded as working hypotheses Whatever the mechanism is, we trust to have adduced adequate reasons for our contention that extrasystolic impulse formation should be separated from the automatic one. The former yield propagated impulses *only* during a certain period of enhanced excitability consequent upon an initiating beat, in the latter the ectopic impulse formation is independent of such other beat

The first meaning given in the *Oxford Dictionary* for αὐτόματ-ος is " Self-acting, having the power of motion or action within itself". Clearly, no biological phenomenon dependent on another phenomenon of the same kind, and initiated by it with a constant time sequence and in a definite, though as yet only imperfectly understood manner can thus be called " automatic "

SUMMARY

The thesis is put forward that true *extrasystoles,* that is, ectopic beats with accurate coupling to the preceding beat (and often with constant shape) in the electrocardiogram are precipitated in the ectopic centre by an initiating beat and are thus a passive, derivative phenomenon, as distinct from those forms of ectopic arrhythmia in which two (or more) independent automatic centres, of equal importance, of impulse formation co-exist, the activity of neither of which is deriving from that of the other. For this reason we advocate that true extrasystoles should be separated from automatic ectopic arrhythmias (for instance parasystole)

Alternative hypotheses are discussed which have been put forward to explain extrasystoles, namely the conception of a parasystolic origin of extrasystoles, and that of a circus movement as the underlying mechanism. The arguments, on which these views are based, are discussed and reasons adduced why we consider these hypotheses to be unsatisfactory explanations.

The work is reviewed in some detail which demonstrates that extrasystoles arise in one circumscribed focus, and that their origin there is dependent on an initiating beat. Reasons are given for the statement that the origin of extrasystoles in such a centre is not due to increased automatism of the ectopic focus. While the separation between extrasystolic and automatic ectopic impulse formation is stressed it is pointed out that, in rare instances, the same focus may give rise to extrasystolic *and* automatic ectopic beats.

Any views about the physiological processes underlying extrasystolic and automatic impulse formation have to be consistent with the observations that

(1) these two varieties of ectopic beats mostly occur independently from one another, and
(2) in some, comparatively rare, instances these two varieties have been observed to be related to one another in various ways

It is pointed out that our knowledge about this subject is very scanty, but that more recent advances in cardiac and nervous physiology have thrown some light on this problem. It is emphasized that observations made on one kind of tissue can only with the greatest reserve be applied to another, but that analogies in the initiation and conduction of impulses *in living tissue exist which may show the way in which a fuller understanding may be sought.*

From this point of view some relevant physiological data about initiation and propagation of excitation are reviewed, based on the membrane theory. Some relevant work on [illegible]

observations demonstrating an increase in excitability after a propagated disturbance, which may last for a considerable time The local, graduated, non-propagated changes in potential at the site of origin of a propagated impulse are described, as they were established in nerve and skeletal and cardiac muscle.

The repetitive response to a constant stimulus has been observed in various experimental conditions and examples are discussed of this phenomenon resulting from injury, electrical and chemical stimulation The bearing which such observations have in emphasizing the rôle of metabolic factors in the origin of extrasystoles is pointed out.

Such observations are considered to support the hypothesis that true extrasystoles arise, in a circumscribed focus, as the result of sub-threshold activity in the ectopic centre temporarily becoming supra-threshold during the period of enhanced excitability consequent upon the initiating beat It is pointed out that the supernormal phase, while being of para*mount importance in the causation of such temporarily increased excitability, is not the* only factor, and that the local potential changes in the centre are likely to exert a profound influence on the time of occurrence of the extrasystole

It is emphasized that, whatever the finer mechanism is which produces the extrasystole, no circus movement, but impulse formation in a circumscribed centre is assumed

Regarding automatic impulse formation, in particular parasystole, it is pointed out that the main difficulty centres around the mechanism of the protection of the ectopic focus against the impulses of the co-existent pacemaker. The conception of a block zone, spherically surrounding the centre, while possibly accounting for some instances, is unsatisfactory as a general explanation for reasons pointed out in the chapter on pararrhythmias We *visualize such protection as due to reduced excitability of the* ectopic focus The difficulties in reconciling this view with the membrane theory are briefly discussed and it is pointed out, by way of a hypothetical assumption, that more recent work on acetylcholine seems to indicate that a biochemical disorder may be the underlying condition In cases of parasystole with a fast ectopic rhythm the high rate itself accounts for the protection of the centre and no further mechanism need be assumed.

An attempt is made at explaining those instances in which a relationship between extrasystoles and automatic beats has been observed, namely: automatic beats originating in the same focus as extrasystoles; automatic beats followed by extrasystoles arising in the same centre; and transition from parasystole into an extrasystolic arrhythmia.

In conclusion it is emphasized that our views about the mechanism underlying extrasystolic and automatic impulse formation should only be regarded as working hypotheses, but that we trust to have adduced cogent reasons for our contention that these two varieties of ectopic arrhythmias should be considered as fundamentally different.

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similar institution established in Scotland. Not only would such a centre give employment to many of our amputees but it would stimulate local interest in their welfare. It would also be a wise insurance against having all our eggs in one basket in times of war.

I wish to express my thanks to my two assistants, Mr Thomson and Mr McSwan, for their help in interviewing patients and to J. G. Hanger & Co. Ltd, and Hugh Steeper Ltd., for supplying me with demonstration artificial limbs and appliances.

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